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| **Table S1.** Stratified Analysis of *TS* gene polymorphisms for combined clinical factors in CAD patients and control subjects | | | | | | | | | |
|  |  | ***TSER 2R/3R*** | | ***TS* 1100T>C** | | ***TS* 1170A>G** |  | ***TS* 1494ins/del** |  |
| **Variables** | **Model** | **AOR (95% CI)** | ***P*** | **AOR (95% CI)** | ***P*** | **AOR (95% CI)** | ***P*** | **AOR (95% CI)** | ***P*** |
| Age |  |  |  |  |  |  |  |  |  |
| ≤63years | Dominant | 0.668 (0.419-1.066) | 0.091 | 1.210 (0.786-1.864) | 0.387 | 0.837 (0.541-1.295) | 0.425 | 0.864 (0.561-1.330) | 0.507 |
|  | Recessive | 1.284 (0.270-6.119) | 0.753 | 1.326 (0.669-2.628) | 0.419 | 0.328 (0.123-0.878) | 0.026 | 0.958 (0.484-1.897) | 0.903 |
| >63years | Dominant | 1.133 (0.737-1.744) | 0.569 | 1.293 (0.880-1.899) | 0.191 | 0.671 (0.454-0.991) | 0.045 | 0.816 (0.556-1.199) | 0.301 |
|  | Recessive | 1.200 (0.291-4.956) | 0.801 | 1.065 (0.482-2.356) | 0.876 | 0.708 (0.317-1.583) | 0.401 | 0.799 (0.378-1.688) | 0.556 |
| Gender |  |  |  |  |  |  |  |  |  |
| male | Dominant | 0.982 (0.589-1.639) | 0.945 | 1.812 (0.868-3.783) | 0.113 | 0.510 (0.317-0.819) | 0.005 | 0.694 (0.436-1.104) | 0.123 |
|  | Recessive | 1.324 (0.278-6.303) | 0.724 | 1.812 (0.868-3.783) | 0.113 | 0.277 (0.086-0.893) | 0.032 | 1.056 (0.502-2.221) | 0.885 |
| female | Dominant | 0.907 (0.606-1.358) | 0.636 | 1.440 (0.992-2.089) | 0.055 | 0.890 (0.614-1.290) | 0.538 | 1.043 (0.721-1.509) | 0.823 |
|  | Recessive | 1.349 (0.327-5.556) | 0.679 | 0.805 (0.381-1.698) | 0.569 | 0.613 (0.290-1.295) | 0.200 | 0.873 (0.441-1.726) | 0.696 |
| HTN |  |  |  |  |  |  |  |  |  |
| No | Dominant | 0.668 (0.427-1.045) | 0.077 | 1.324 (0.889-1.972) | 0.167 | 0.915 (0.611-1.371) | 0.667 | 0.794 (0.534-1.181) | 0.254 |
|  | Recessive | 1.895 (0.476-7.540) | 0.364 | 1.226 (0.609-2.470) | 0.568 | 0.558 (0.236-1.322) | 0.185 | 0.833 (0.400-1.732) | 0.624 |
| Yes | Dominant | 1.310 (0.828-2.072) | 0.249 | 1.307 (0.859-1.989) | 0.212 | 0.555 (0.363-0.848) | 0.007 | 0.966 (0.635-1.469) | 0.872 |
|  | Recessive | 0.523 (0.109-2.503) | 0.417 | 1.283 (0.595-2.768) | 0.526 | 0.445 (0.182-1.088) | 0.076 | 0.991 (0.490-2.006) | 0.980 |
| DM |  |  |  |  |  |  |  |  |  |
| No | Dominant | 0.924 (0.653-1.308) | 0.657 | 1.224 (0.892-1.680) | 0.211 | 0.855 (0.622-1.177) | 0.337 | 0.810 (0.591-1.112) | 0.192 |
|  | Recessive | 0.943 (0.315-2.824) | 0.916 | 1.068 (0.597-1.908) | 0.825 | 0.484 (0.234-1.001) | 0.050 | 0.763 (0.431-1.350) | 0.353 |
| Yes | Dominant | 0.961 (0.459-2.013) | 0.916 | 1.770 (0.884-3.544) | 0.107 | 0.323 (0.155-0.674) | 0.003 | 1.239 (0.628-2.446) | 0.537 |
|  | Recessive | N/A | 0.998 | 1.890 (0.556-6.419) | 0.308 | 0.551 (0.162-1.870) | 0.339 | 1.782 (0.531-5.978) | 0.350 |
| Lipid |  |  |  |  |  |  |  |  |  |
| No | Dominant | 0.833 (0.583-1.191) | 0.317 | 1.231 (0.885-1.711) | 0.217 | 0.757 (0.542-1.057) | 0.102 | 0.941 (0.677-1.308) | 0.716 |
|  | Recessive | 0.953 (0.273-3.328) | 0.939 | 1.296 (0.729-2.303) | 0.377 | 0.480 (0.228-1.014) | 0.054 | 1.036 (0.582-1.845) | 0.903 |
| Yes | Dominant | 1.273 (0.656-2.467) | 0.475 | 1.432 (0.794-2.585) | 0.233 | 0.699 (0.392-1.245) | 0.224 | 0.673 (0.375-1.207) | 0.184 |
|  | Recessive | 1.632 (0.259-10.304) | 0.602 | 0.836 (0.271-2.574) | 0.754 | 0.598 (0.199-1.797) | 0.360 | 0.568 (0.202-1.598) | 0.284 |
| Smoking status | |  |  |  |  |  |  |  |  |
| No | Dominant | 1.146 (0.788-1.666) | 0.477 | 1.138 (0.809-1.600) | 0.457 | 0.715 (0.507-1.007) | 0.055 | 0.845 (0.601-1.188) | 0.333 |
|  | Recessive | 1.236 (0.358-4.271) | 0.738 | 0.937 (0.483-1.819) | 0.848 | 0.457 (0.219-0.956) | 0.038 | 0.859 (0.461-1.600) | 0.632 |
| Yes | Dominant | 0.555 (0.301-1.021) | 0.058 | 2.016 (1.159-3.507) | 0.013 | 0.736 (0.421-1.285) | 0.281 | 1.014 (0.592-1.739) | 0.959 |
|  | Recessive | 0.935 (0.139-6.273) | 0.945 | 1.914 (0.847-4.326) | 0.119 | 0.583 (0.183-1.857) | 0.361 | 1.064 (0.457-2.475) | 0.886 |
| Homocysteine |  |  |  |  |  |  |  |  |  |
| ≤11.40μmol/l | Dominant | 0.848 (0.590-1.217) | 0.370 | 1.203 (0.864-1.675) | 0.274 | 0.703 (0.502-0.985) | 0.041 | 0.843 (0.606-1.174) | 0.312 |
|  | Recessive | 1.771 (0.578-5.431) | 0.317 | 1.216 (0.675-2.190) | 0.515 | 0.157 (0.052-0.471) | 0.001 | 0.820 (0.464-1.449) | 0.494 |
| >11.40μmol/l | Dominant | 0.992 (0.508-1.936) | 0.981 | 1.566 (0.852-2.881) | 0.149 | 0.695 (0.383-1.260) | 0.231 | 0.928 (0.509-1.692) | 0.808 |
|  | Recessive | N/A | 0.998 | 1.370 (0.467-4.023) | 0.567 | 1.063 (0.393-2.874) | 0.904 | 1.528 (0.507-4.607) | 0.452 |
| Folate |  |  |  |  |  |  |  |  |  |
| ≥4.85ng/ml | Dominant | 0.787 (0.537-1.155) | 0.222 | 1.350 (0.955-1.909) | 0.089 | 0.679 (0.480-0.961) | 0.029 | 0.949 (0.673-1.340) | 0.768 |
|  | Recessive | 1.539 (0.447-5.294) | 0.495 | 1.236 (0.669-2.286) | 0.499 | 0.425 (0.188-0.961) | 0.040 | 0.978 (0.548-1.746) | 0.941 |
| <4.85ng/ml | Dominant | 1.274 (0.666-2.436) | 0.464 | 1.248 (0.688-2.265) | 0.467 | 0.913 (0.494-1.686) | 0.771 | 1.015 (0.557-1.848) | 0.962 |
|  | Recessive | 1.609 (0.151-17.161) | 0.694 | 1.430 (0.448-4.566) | 0.547 | 0.345 (0.094-1.265) | 0.108 | 1.229 (0.335-4.504) | 0.756 |
| Adjusted by age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoke. | | | | | | | | | |

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| **Table S2.** Adjusted odds ratios for CAD risk associated with *TS* gene polymorphisms, combined by clinical factors | | | | | | | | | | | | |
| **Characteristics** | ***TSER*** |  | | ***TS* 1100T>C** | |  | | ***TS* 1170A>G** |  | | ***TS* 1494 0bp/6bp** | |
| **3R3R** | **3R2R+2R2R** |  | **TT** | | **TC+CC** |  | **AA** | **AG+GG** |  | **0bo0bp** | **0bp6bp+6bp6bp** |
| Age |  |  |  |  | |  |  |  |  |  |  |  |
| ≤63years | 1.000 (reference) | 0.668 (0.419-1.066) |  | 1.000 (reference) | | 1.210 (0.786-1.864) |  | 1.000 (reference) | 0.837 (0.541-1.295) |  | 1.000 (reference) | 0.864 (0.561-1.330) |
| >63years | 0.876 (0.621-1.234) | 1.010 (0.637-1.600) |  | 0.962 (0.628-1.471) | | 1.290 (0.845-1.967) |  | 1.093 (0.718-1.665) | 0.752 (0.493-1.147) |  | 1.033 (0.677-1.575) | 0.813 (0.532-1.244) |
| Gender |  |  |  |  | |  |  |  |  |  |  |  |
| male | 1.000 (reference) | 0.982 (0.589-1.639) |  | 1.000 (reference) | | 1.150 (0.727-1.818) |  | 1.000 (reference) | 0.510 (0.317-0.819) |  | 1.000 (reference) | 0.694 (0.436-1.104) |
| female | 0.768 (0.512-1.155) | 0.652 (0.407-1.046) |  | 0.464 (0.275-0.784) | | 0.623 (0.381-1.018) |  | 0.403 (0.252-0.644) | 0.518 (0.321-0.836) |  | 0.441 (0.260-0.748) | 0.404 (0.245-0.667) |
| Hypertension |  |  |  |  | |  |  |  |  |  |  |  |
| No | 1.000 (reference) | 0.668 (0.427-1.045) |  | 1.000 (reference) | | 1.324 (0.889-1.972) |  | 1.000 (reference) | 0.915 (0.611-1.371) |  | 1.000 (reference) | 0.794 (0.534-1.181) |
| Yes | 1.378 (0.979-1.941) | 1.661 (1.050-2.630) |  | 1.664 (1.087-2.546) | | 2.122 (1.401-3.215) |  | 1.797 (1.176-2.745) | 1.172 (0.764-1.796) |  | 1.524 (0.992-2.342) | 1.406 (0.942-2.099) |
| Diabetes mellitus |  |  |  |  | |  |  |  |  |  |  |  |
| No | 1.000 (reference) | 0.924 (0.653-1.308) |  | 1.000 (reference) | | 1.224 (0.892-1.680) |  | 1.000 (reference) | 0.855 (0.622-1.177) |  | 1.000 (reference) | 0.810 (0.591-1.112) |
| Yes | 2.865 (1.841-4.458) | 2.414 (1.277-4.564) |  | 2.394 (1.405-4.079) | | 3.996 (2.329-6.855) |  | 4.239 (2.362-7.609) | 1.695 (1.013-2.836) |  | 2.421 (1.423-4.117) | 2.963 (1.721-5.102) |
| Hyperlipidemia |  |  |  |  | |  |  |  |  |  |  |  |
| No | 1.000 (reference) | 0.833 (0.583-1.191) |  | 1.000 (reference) | | 1.231 (0.885-1.711) |  | 1.000 (reference) | 0.757 (0.542-1.057) |  | 1.000 (reference) | 0.941 (0.677-1.308) |
| Yes | 1.245 (0.852-1.820) | 1.390 (0.770-2.509) |  | 1.372 (0.865-2.175) | | 1.861 (1.134-3.054) |  | 1.495 (0.932-2.397) | 1.037 (0.640-1.680) |  | 1.632 (1.027-2.591) | 1.066 (0.657-1.730) |
| Smoking |  |  |  |  | |  |  |  |  |  |  |  |
| No | 1.000 (reference) | 1.146 (0.788-1.666) |  | 1.000 (reference) | | 1.138 (0.809-1.600) |  | 1.000 (reference) | 0.715 (0.507-1.007) |  | 1.000 (reference) | 0.845 (0.601-1.188) |
| Yes | 0.875 (0.566-1.351) | 0.504 (0.278-0.914) |  | 0.407 (0.231-0.717) | | 0.724 (0.435-1.205) |  | 0.541 (0.336-0.871) | 0.484 (0.272-0.860) |  | 0.496 (0.284-0.868) | 0.463 (0.277-0.774) |
| Homocysteine |  |  |  |  | |  |  |  |  |  |  |  |
| ≤11.40μmol/l | 1.000 (reference) | 0.888 (0.622-1.268) |  | 1.000 (reference) | | 1.180 (0.852-1.635) |  | 1.000 (reference) | 0.746 (0.535-1.039) |  | 1.000 (reference) | 0.833 (0.602-1.154) |
| >11.40μmol/l | 1.129 (0.752-1.695) | 1.106 (0.596-2.050) |  | 0.901 (0.540-1.504) | | 1.484 (0.905-2.433) |  | 1.038 (0.631-1.707) | 0.749 (0.452-1.240) |  | 0.972 (0.584-1.618) | 0.948 (0.580-1.550) |
| Folate |  |  |  |  | |  |  |  |  |  |  |  |
| ≥4.85ng/ml | 1.000 (reference) | 0.791 (0.550-1.137) |  | | 1.000 (reference) | 1.279 (0.920-1.778) |  | 1.000 (reference) | 0.697 (0.501-0.970) |  | 1.000 (reference) | 0.831 (0.598-1.153) |
| <4.85ng/ml | 1.590 (1.053-2.399) | 2.250 (1.243-4.071) |  | 1.968 (1.182-3.277) | | 2.621 (1.585-4.333) |  | 1.698 (1.036-2.783) | 1.420 (0.859-2.348) |  | 1.621 (0.979-2.685) | 1.792 (1.089-2.947) |
| HDL-cholesterol |  |  |  |  | |  |  |  |  |  |  |  |
| ≥40(M), 50(F) | 1.000 (reference) | 0.468 (0.253-0.865) |  | 1.000 (reference) | | 0.941 (0.546-1.623) |  | 1.000 (reference) | 1.442 (0.819-2.538) |  | 1.000 (reference) | 0.648 (0.373-1.125) |
| <40(M), 50(F) | 1.267 (0.789-2.035) | 1.585 (0.852-2.950) |  | 1.135 (0.640-2.014) | | 2.471 (1.294-4.717) |  | 2.556 (1.460-4.477) | 1.565 (0.877-2.792) |  | 1.331 (0.735-2.410) | 1.387 (0.759-2.535) |
| Adjusted by age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoke.  Abbreviations: HDL-cholesterol; high density lipoprotein-cholesterols | | | | | | | | | | | | |

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| **Table S3.** The 4 site haplotype analysis for *TS* gene polymorphisms in CAD patients and control subjects. | | | | |
| **Haplotype** | **Control (2n=854)** | **CAD (2n=848)** | **OR (95% CI)** | ***P*a** |
| *TSER*/*TS*1100/1170/1494 | |  |  |  |
| 3R-T-A-0bp | 0.3554 | 0.3916 | 1.000 (reference) |  |
| 3R-T-A-6bp | 0.0250 | 0.0199 | 0.778 (0.400-1.514) | 0.501 |
| 3R-T-G-6bp | 0.0020 | 0.0038 | 1.373 (0.228-8.279) | 1.000 |
| 3R-C-A-6bp | 0.1744 | 0.1621 | 0.836 (0.633-1.106) | 0.227 |
| 3R-C-G-0bp | - | 0.0036 | 6.411 (0.330-124.700) | 0.251 |
| 3R-C-G-6bp | - | - | - | - |
| 2R-T-A-0bp | 0.0371 | 0.0242 | 0.601 (0.339-1.065) | 0.087 |
| 2R-T-A-6bp | 0.0087 | 0.0073 | 0.687 (0.236-2.002) | 0.593 |
| 2R-T-G-0bp | 0.0085 | 0.0188 | 2.093 (0.849-5.158) | 0.136 |
| 2R-T-G-6bp | 0.0019 | 0.0015 | 0.458 (0.041-5.078) | 0.609 |
| 2R-C-A-0bp | 0 | - | - | - |
| 2R-C-A-6bp | 0.1053 | 0.0984 | 0.844 (0.603-1.182) | 0.346 |
| 2R-C-G-0bp | 0.0012 | 0 | 0.305 (0.012-7.528) | 0.479 |
| 2R-C-G-6bp | - | 0.0042 | 8.242 (0.442-153.800) | 0.126 |
| Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; TSER, thymidylate synthase enhancer region; TS, thymidylate synthase; FDR, false discovery rate. | | | | |
| a *P*-value calculated by chi-square test and fisher's exact test. The *P*-value<0.05 showed the bold type in Table 3. | | | | |

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| **Table S4.** The 3 site haplotype analysis for *TS* gene polymorphisms CAD patients and control subjects. | | | | |
| **Haplotype** | **Control (2n=854)** | **CAD (2n=848)** | **OR (95% CI)** | ***P*a** |
| *TSER*/*TS*1100/1170 | |  |  |  |
| 3R-T-A | 0.3781 | 0.4148 | 1.000 (Reference) |  |
| 3R-C-A | 0.1798 | 0.2118 | 1.073 (0.825 - 1.395) | 0.601 |
| 3R-C-G | - | 0.0058 | 10.100 (0.556 - 183.400) | 0.063 |
| 2R-T-G | 0.01 | 0.0218 | 1.835 (0.813 - 4.143) | 0.117 |
| 2R-C-A | 0.1026 | 0.0975 | 0.865 (0.619 - 1.211) | 0.399 |
| 2R-C-G | 0.0022 | 0.0045 | 1.835 (0.334 - 10.090) | 0.688 |
| *TSER*/*TS*1100/1494 | |  |  |  |
| 3R-T-0bp | 0.6336 | 0.6049 | 1.000 (Reference) |  |
| 3R-T-6bp | 0.0253 | 0.0238 | 0.959 (0.517 - 1.778) | 0.893 |
| 3R-C-6bp | 0.1746 | 0.1618 | 0.970 (0.746 - 1.260) | 0.817 |
| 2R-T-0bp | 0.0454 | 0.0429 | 0.973 (0.609 - 1.556) | 0.910 |
| 2R-T-6bp | 0.0111 | 0.0088 | 0.820 (0.303 - 2.219) | 0.694 |
| 2R-C-0bp | 0 | 0 | - | - |
| 2R-C-6bp | 0.1063 | 0.1028 | 1.008 (0.734 - 1.385) | 0.960 |
| *TSER*/*TS*1170/1494 | |  |  |  |
| 3R-A-0bp | 0.3592 | 0.4487 | 1.000 (Reference) |  |
| 3R-G-6bp | 0.0034 | 0.0067 | 1.616 (0.401 - 6.516) | 0.738 |
| 2R-G-0bp | 0.0098 | 0.0202 | 1.717 (0.731 - 4.032) | 0.183 |
| *TS*1100/1170/1494 | |  |  |  |
| T-A-0bp | 0.392 | 0.4153 | 1.000 (Reference) |  |
| T-A-6bp | 0.0331 | 0.0273 | 0.782 (0.441 - 1.384) | 0.395 |
| T-G-6bp | 0.0033 | 0.0053 | 1.269 (0.282 - 5.714) | 1.000 |
| C-A-6bp | 0.2809 | 0.2612 | 0.876 (0.692 - 1.110) | 0.273 |
| C-G-0bp | 0.0012 | 0.004 | 2.855 (0.295 - 27.600) | 0.625 |
| C-G-6bp | - | 0.0034 | 6.662 (0.343 - 129.600) | 0.250 |
| Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; TSER, thymidylate synthase enhancer region; TS, thymidylate synthase; FDR, false discovery rate. | | | | |
| a *P*-value calculated by chi-square test and fisher's exact test. The *P*-value<0.05 showed the bold type in Table 3. | | | | |

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| **Table S5.** The 2 site haplotype analysis for *TS* gene polymorphisms in CAD patients and control subjects. | | | | |
| **Haplotype** | **Control (2n=854)** | **CAD (2n=848)** | **OR (95% CI)** | ***P*a** |
| *TSER*/*TS*1100 | |  |  |  |
| 3R-T | 0.6569 | 0.6282 | 1.000 (Reference) |  |
| 3R-C | 0.1804 | 0.2173 | 1.258 (0.985 - 1.606) | 0.065 |
| 2R-T | 0.0586 | 0.0522 | 0.926 (0.607 - 1.413) | 0.722 |
| 2R-C | 0.1042 | 0.1023 | 1.029 (0.748 - 1.415) | 0.861 |
| *TSER*/*TS* 1494 | |  |  |  |
| 3R-0bp | 0.6371 | 0.66 | 1.000 (Reference) |  |
| 3R-6bp | 0.2002 | 0.1855 | 0.892 (0.697 - 1.141) | 0.363 |
| 2R-0bp | 0.0456 | 0.0428 | 0.897 (0.561 - 1.432) | 0.648 |
| 2R-6bp | 0.1172 | 0.1117 | 0.923 (0.681 - 1.251) | 0.605 |
| *TS* 1100/1170 | |  |  |  |
| T-A | 0.4259 | 0.4452 | 1.000 (Reference) |  |
| C-A | 0.2826 | 0.3095 | 1.047 (0.835 - 1.313) | 0.692 |
| *TS* 1100/1494 | |  |  |  |
| T-0bp | 0.679 | 0.6478 | 1.000 (Reference) |  |
| T-6bp | 0.0364 | 0.0326 | 0.954 (0.565 - 1.612) | 0.861 |
| C-6bp | 0.2809 | 0.2645 | 0.986 (0.794 - 1.224) | 0.899 |
| Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; TSER, thymidylate synthase enhancer region; TS, thymidylate synthase; FDR, false discovery rate. | | | | |
| a *P*-value calculated by chi-square test and fisher's exact test. The *P*-value<0.05 showed the bold type in Table 3. | | | | |

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| **Table S6.** Genotype combination analyses for the *TS* gene polymorphisms in CAD patients and controls | | | | |
| **Genotype combinations** | **Controls** | **CAD** | **AOR (95% CI)** | ***P\**** |
| **(n=427)** | **(n=424)** |
| *TSER*/*TS* 1100T>C | | | | |
| 3R3R/TT | 182 (42.6) | 166 (39.2) | 1.000 (reference) |  |
| 3R3R/TC | 99 (23.2) | 110 (25.9) | 1.259 (0.880 - 1.801) | 0.207 |
| 3R3R/CC | 15 (3.5) | 25 (5.9) | 1.927 (0.951 - 3.906) | 0.069 |
| 2R3R/TT | 33 (7.7) | 27 (6.4) | 0.847 (0.467 - 1.534) | 0.583 |
| 2R3R/TC | 75 (17.6) | 75 (17.7) | 1.142 (0.753 - 1.732) | 0.533 |
| 2R3R/CC | 15 (3.5) | 13 (3.1) | 0.705 (0.301 - 1.653) | 0.421 |
| 2R2R/TT | 2 (0.5) | 1 (0.2) | 0.652 (0.053 - 8.053) | 0.739 |
| 2R2R/TC | 3 (0.7) | 4 (0.9) | 1.718 (0.365 - 8.079) | 0.493 |
| 2R2R/CC | 3 (0.7) | 3 (0.7) | 1.021 (0.174 - 6.003) | 0.982 |
| *TSER*/*TS* 1170A>G | | | | |
| 3R3R/AA | 130 (30.4) | 164 (38.7) | 1.000 (reference) |  |
| 2R3R/AG | 46 (10.8) | 47 (11.1) | 0.731 (0.435 - 1.229) | 0.238 |
| 2R3R/GG | 3 (0.7) | 3 (0.7) | 0.865 (0.161 - 4.651) | 0.866 |
| 2R2R/AA | 7 (1.6) | 5 (1.2) | 0.611 (0.169 - 2.214) | 0.453 |
| 2R2R/AG | 1 (0.2) | 3 (0.7) | 2.368 (0.235 - 23.905) | 0.465 |
| 2R2R/GG | 0 (0.0) | 0 (0.0) | - | - |
| *TSER*/*TS* 1494ins>del | | | | |
| 3R3R/0bp0bp | 170 (39.8) | 187 (44.1) | 1.000 (reference) |  |
| 3R3R/0bp6bp | 107 (25.1) | 95 (22.4) | 0.819 (0.572 - 1.173) | 0.277 |
| 3R3R/6bp6bp | 19 (4.4) | 19 (4.5) | 0.971 (0.485 - 1.945) | 0.934 |
| 2R3R/0bp0bp | 24 (5.6) | 23 (5.4) | 0.802 (0.419 - 1.539) | 0.508 |
| 2R3R/0bp6bp | 82 (19.2) | 75 (17.7) | 0.881 (0.587 - 1.323) | 0.542 |
| 2R3R/6bp6bp | 17 (4.0) | 17 (4.0) | 0.709 (0.328 - 1.534) | 0.382 |
| 2R2R/0bp0bp | 1 (0.2) | 1 (0.2) | 1.581 (0.083 - 30.228) | 0.761 |
| 2R2R/0bp6bp | 4 (0.9) | 4 (0.9) | 0.924 (0.221 - 3.873) | 0.914 |
| 2R2R/6bp6bp | 3 (0.7) | 3 (0.7) | 0.925 (0.157 - 5.460) | 0.932 |
| *TS* 1100T>C/*TS* 1170A>G | | | | |
| TT/AA | 70 (16.4) | 86 (20.3) | 1.000 (reference) |  |
| TC/AA | 109 (25.5) | 109 (25.7) | 0.866 (0.550 - 1.363) | 0.534 |
| TC/AG | 68 (15.9) | 78 (18.4) | 0.837 (0.511 - 1.370) | 0.479 |
| TC/GG | 0 (0.0) | 2 (0.5) | - | 0.995 |
| CC/AA | 32 (7.5) | 39 (9.2) | 0.841 (0.442 - 1.602) | 0.599 |
| CC/AG | 1 (0.2) | 2 (0.5) | 1.973 (0.141 - 27.593) | 0.614 |
| CC/GG | 0 (0.0) | 0 (0.0) | - | - |
| *TS* 1100T>C/*TS* 1494ins>del | | | | |
| TT/0bp0bp | 194 (45.4) | 180 (42.5) | 1.000 (reference) |  |
| TT/0bp6bp | 18 (4.2) | 8 (1.9) | 0.492 (0.199 - 1.214) | 0.124 |
| TT/6bp6bp | 5 (1.2) | 6 (1.4) | 1.513 (0.414 - 5.528) | 0.531 |
| TC/0bp6bp | 173 (40.5) | 162 (38.2) | 1.053 (0.772 - 1.436) | 0.745 |
| TC/6bp6bp | 3 (0.7) | 6 (1.4) | 1.853 (0.432 - 7.953) | 0.407 |
| CC/0bp0bp | 0 (0.0) | 10 (2.4) | - | 0.995 |
| CC/0bp6bp | 2 (0.5) | 4 (0.9) | 2.752 (0.461 - 16.411) | 0.267 |
| CC/6bp6bp | 31 (7.3) | 27 (6.4) | 0.871 (0.479 - 1.582) | 0.650 |
| *TS* 1170A>G/*TS* 1494ins>del | | | | |
| AA/0bp0bp | 57 (13.3) | 101 (23.8) | 1.000 (reference) |  |
| AG/6bp6bp | 2 (0.5) | 3 (0.7) | 1.140 (0.145 - 8.972) | 0.901 |
| GG/0bp6bp | 0 (0.0) | 2 (0.5) | - | 0.995 |
| GG/6bp6bp | 0 (0.0) | 0 (0.0) | - | - |
| Abbreviation: AOR, adjusted odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; TS, thymidylate synthase. \*Adjusted by age, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking. The *P*-values <0.05 showed the bold type in Table 4 | | | | |

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| **Table S7.** Baseline characteristics between controls and CAD patients in sample 1 and 2 | | | | | | |
| **Characteristic** | **Sample 1\*** | | | **Sample 2\*\*** | | |
| **Controls  (n=288)** | **CAD patients (n=166)** | ***P*** | **Controls  (n=139)** | **CAD patients (n=251)** | ***P*** |
| Male (n, %) | 95 (33.0) | 58 (34.9) | 0.766 | 73 (52.5) | 96 (38.2) | 0.091 |
| Age (years, mean ± SD) | 61.22±11.59 | 64.13±9.91 | 0.019a | 61.88±11.42 | 61.47±10.42 | 0.724 |
| Hypertension (n, %) | 114 (39.6) | 92 (55.4) | 0.048 | 57 (41.0) | 133 (53.0) | 0.178 |
| Diabetes mellitus (n, %) | 36 (12.5) | 62 (37.3) | <0.0001 | 15 (10.8) | 55 (21.9) | 0.020 |
| Hyperlipidemia (n, %) | 68 (23.6) | 44 (26.5) | 0.593 | 29 (20.9) | 71 (28.3) | 0.212 |
| Smoking (n, %) | 75 (26.0) | 45 (27.1) | 0.850 | 61 (43.9) | 61 (24.3) | 0.005 |
| Body mass index (kg/cm2, mean ± SD) | 24.27±3.34 | 24.85±3.15 | 0.096 | 24.26±3.35 | 25.44±3.13 | 0.001 |
| Fasting blood sugar (mg/dL, mean ± SD) | 110.42±35.02 | 153.61±70.51 | <0.0001a | 115.11±31.55 | 133.80±58.45 | <0.001a |
| HbA1c (%, mean ± SD) | 6.58±1.61 | 7.09±1.80 | 0.143 | 5.87±0.82 | 6.49±3.43 | 0.101a |
| HDL-C (mg/dl, mean ± SD) | 46.18±16.18 | 41.69±10.17 | 0.056a | 47.78±11.47 | 45.11±12.27 | 0.082 |
| LDL-C (mg/dl, mean ± SD) | 128.73±52.24 | 116.35±37.46 | 0.161a | 114.70±32.35 | 109.28±38.39 | 0.249 |
| Total cholesterol (mg/dl, mean ± SD) | 196.25±40.05 | 189.03±45.68 | 0.023a | 189.59±33.74 | 184.64±44.59 | 0.124a |
| Triglyceride (mg/dl, mean ± SD) | 149.07±91.82 | 164.88±99.82 | 0.092 | 128.38±73.96 | 150.36±95.68 | 0.006a |
| Hcy (μmol/L, mean ± SD) | 9.41±3.37 | 10.62±4.21 | 0.001a | 10.50±4.74 | 9.52±5.57 | 0.001a |
| Folate (nmol/L, mean ± SD) | 9.28±8.31 | 10.51±14.34 | 0.551a | 8.87±7.17 | 7.59±5.27 | 0.019a |
| *P-values* were calculated by two-sided t-test for continuous variables and chi-square test for categorical variables. a P-values were calculated by Mann-Whitney test for continuous variables. CAD, coronary artery disease; SD, standard deviation; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; Hcy, homocysteine; HbA1c, hemoglobin A1c. \* Sample 1 was recruited from 2000 to 2006. \*\* Sample 2 was recruited from 2007 to 2012. | | | | | | |

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| **Table S8.** Genotype frequencies of *TS* gene polymorphisms between CAD patients and control subjects in samples 1 and 2 | | | | | | | | |
| **Genotypes** | **Sample 1\*\*** | | | | **Sample 2\*\*\*** | | | |
| **Controls  (n=288)** | **CAD patients (n=166)** | **AOR (95% CI)\*** | ***P*a** | **Controls  (n=139)** | **CAD patients (n=251)** | **AOR (95% CI)\*** | ***P*a** |
| *TSER* 2R/3R |  |  |  |  |  |  |  |  |
| 3R3R | 205 (71.2) | 119 (71.7) | 1.000 (reference) |  | 91 (65.5) | 175 (69.7) | 1.000 (reference) |  |
| 2R3R | 80 (27.8) | 46 (27.7) | 1.044 (0.654 - 1.665) | 0.857 | 43 (30.9) | 69 (27.5) | 0.799 (0.489 - 1.305) | 0.370 |
| 2R2R | 3 (1.0) | 1 (0.6) | 1.129 (0.100 - 12.707) | 0.922 | 5 (3.6) | 7 (2.8) | 0.786 (0.233 - 2.658) | 0.699 |
| Dominant model |  |  | 1.045 (0.658 - 1.660) | 0.852 |  |  | 0.793 (0.495 - 1.271) | 0.336 |
| Recessive model |  |  | 1.042 (0.095 - 11.393) | 0.973 |  |  | 0.794 (0.235 - 2.688) | 0.711 |
| *TS* 1100T>C |  |  |  |  |  |  |  |  |
| TT | 150 (52.1) | 63 (38.0) | 1.000 (reference) |  | 67 (48.2) | 126 (50.2) | 1.000 (reference) |  |
| TC | 118 (41.0) | 80 (48.2) | **1.800 (1.156 - 2.804)** | **0.009** | 59 (42.4) | 107 (42.6) | 0.964 (0.608 - 1.529) | 0.876 |
| CC | 20 (6.9) | 23 (13.9) | **2.741 (1.300 - 5.783)** | **0.008** | 13 (9.4) | 18 (7.2) | 0.732 (0.302 - 1.774) | 0.490 |
| Dominant model |  |  | **1.949 (1.274 - 2.983)** | **0.002** |  |  | 0.937 (0.602 - 1.458) | 0.773 |
| Recessive model |  |  | **2.044 (1.029 - 4.061)** | **0.041** |  |  | 0.790 (0.350 - 1.783) | 0.570 |
| *TS* 1170A>G |  |  |  |  |  |  |  |  |
| AA | 140 (48.6) | 112 (67.5) | 1.000 (reference) |  | 71 (51.1) | 118 (47.0) | 1.000 (reference) |  |
| AG | 124 (43.1) | 47 (28.3) | **0.470 (0.298 - 0.744)** | **0.001** | 59 (42.4) | 123 (49.0) | 1.022 (0.642 - 1.626) | 0.928 |
| GG | 24 (8.3) | 7 (4.2) | **0.341 (0.129 - 0.900)** | **0.030** | 9 (6.5) | 10 (4.0) | 0.492 (0.177 - 1.365) | 0.173 |
| Dominant model |  |  | **0.447 (0.290 - 0.691)** | **0.0003** |  |  | 0.965 (0.617 - 1.511) | 0.877 |
| Recessive model |  |  | 0.481 (0.191 - 1.210) | 0.120 |  |  | 0.575 (0.217 - 1.525) | 0.266 |
| *TS* 1494ins/del |  |  |  |  |  |  |  |  |
| 0bp0bp | 135 (46.9) | 78 (47.0) | 1.000 (reference) |  | 60 (43.2) | 128 (51.0) | 1.000 (reference) |  |
| 0bp6bp | 127 (44.1) | 68 (41.0) | 0.978 (0.632 - 1.512) | 0.920 | 66 (47.5) | 104 (41.4) | 0.750 (0.473 - 1.191) | 0.223 |
| 6bp6bp | 26 (9.0) | 20 (12.0) | 1.286 (0.633 - 2.611) | 0.487 | 13 (9.4) | 19 (7.6) | 0.685 (0.286 - 1.642) | 0.397 |
| Dominant model |  |  | 1.031 (0.681 - 1.560) | 0.887 |  |  | 0.751 (0.482 - 1.170) | 0.205 |
| Recessive model |  |  | 1.270 (0.651 - 2.477) | 0.484 |  |  | 0.839 (0.376 - 1.874) | 0.669 |
| AOR, adjusted odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; TSER, thymidylate synthase enhancer region; TS, thymidylate synthase; HWE, Hardy–Weinberg equilibrium. The *P*-value<0.05 showed the bold type in supplementary table 6. \*The AOR on the basis of risk factors such as age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoking. a *P*-value calculated by multivariable logistic regression. \*\* Sample 1 was recruited from 2000 to 2006. \*\*\* Sample 2 was recruited from 2007 to 2012. | | | | | | | | |

스크린샷, 도표, 디자인, 텍스트이(가) 표시된 사진

자동 생성된 설명**Figure S1.** LD patterns of *TS* gene polymorphisms.The values in the squares denote LD between single markers. (A) Control subjects exhibited strong LD block that *TS* 1100/1170/1494 haplotype. (B) Patients with CAD not exhibited LD block. Dark squares indicate high r2 values and light squares indicate low r2 values. LD, linkage disequilibrium; *TS*, thymidylate synthase; CAD, coronary artery disease.