European Review for Medical and Pharmacological Sciences 2020; 24: 5644-5649

# Correlation between MRAS gene polymorphism and atherosclerosis

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**Abstract. – OBJECTIVE: The aim of this study was to explore the correlation between muscle RAS oncogene homolog (MRAS) gene polymorphism and the onset risk of atherosclerosis (AS).**

**PATIENTS AND METHODS: A total of 135 AS patients diagnosed and treated in our hospital from November 2017 to October 2018 were randomly enrolled in the observation group. Meanwhile, 150 healthy adults were selected as control group. Venous blood was withdrawn from all the subjects, and DNAs were extracted. MRAS gene loci rs9818870 and rs3755751 were analyzed by the multiplex SNaPshot method, and their correlations with the onset risk of AS were explored.**

**RESULTS: No statistically significant differences in the frequencies at gene loci were observed between the two groups ($p$>0.05). Subjects with genotype TT at rs9818870 exhibited significantly higher risk of AS ($p$=0.041<0.05). The recessive model of rs9818870 (GG + AG/AA) in AS patients with coronary heart disease was correlated with AS ($p$=0.048<0.05). Similarly, the dominant model of rs3755751 (TT/TC+CC) in those with hypertension was associated with AS ($p$=0.027<0.05).**

**CONCLUSIONS: MRAS gene is correlated with the onset of AS to a certain degree.**

*Key Words:*
Atherosclerosis (AS), MRAS gene, Gene polymorphism, Correlation.

## Introduction

Atherosclerosis (AS) is a cardiovascular and cerebrovascular disease that can involve large and middle arteries, such as coronary artery, cervical artery, and cerebral artery. AS may affect their elasticity, further leading to lipid deposition, fibrous tissue hyperplasia, and even plaques[1]. AS is caused by the synergy of multiple factors, whose complex pathogenesis remains to be fully clarified. The major risk factors for AS include hypertension, hyperlipidemia, heavy smoking, diabetes mellitus, obesity, and genetics[2]. Gene polymorphism can explain the differences in the risks of diseases in different people due to varying base sites[3]. Now, it has been confirmed that there are many susceptibility genes related to the development of AS. A relevant study has found that AS and coronary artery disease (CAD) share similar risk factors and pathophysiological mechanisms. Meanwhile, their susceptibility genes may be the same[4]. Therefore, the range of research on genes affecting the onset of AS will be greatly widened. Muscle RAS oncogene homolog (MRAS)-encoded M-ras protein has recently been confirmed to be closely associated with the development of hypertension, AS, cerebral infarction, and ischemic stroke[5]. However, there have been few reports on the correlation between MRAS gene and the onset risk of AS in Han Chinese population. Therefore, in this study, the genomes of Han Chinese population were first collected. MRAS gene polymorphic sites were subjected to ABI multiplex SNaPshot genotyping to explore the relationship between gene polymorphism and the onset risk of AS. Our findings might provide basis for the diagnosis and treatment of AS from the genetic aspect.

## Patients and Methods

### Patients

A total of 135 AS patients diagnosed and treated in our hospital from November 2017 to October 2018 were randomly enrolled as observation group. Meanwhile, 150 healthy adults were selected as control group. There were statistically significant differences in age, sex, overweightness, smoking, drinking, hypertension, coronary heart disease, and diabetes between the two groups ($p$<0.05), suggesting that AS was correlated with the above factors (Table I). This study was



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**Table I.** General information.

| Parameter | Observation group (n=135) | Control group (n=150) | Odd ratio (OR), 95% confidence interval (CI) | p |
|---|---|---|---|---|
| Age (year old) | 61.31±7.97 | 55.32±12.01 | | 0.001 |
| Age (year old): ≤44/45-64/≥65 | 10/71/54 | 22/80/48 | | 0.001 |
| Male/female | 95/40 | 88/62 | 1.538, 1.168-2.145 | 0.018 |
| BMI (kg/m2) | 22.45±2.36 | 22.28±2.04 | | 0.401 |
| Overweightness* (n) | 52 | 48 | | 0.157 |
| Smoking (n) | 43 | 30 | 1.845, 1.164-2.846 | 0.007 |
| Drinking (n) | 34 | 23 | 1.817, 1.187-2.984 | 0.019 |
| Hypertension (n) | 27 | 28 | 6.243, 3.997-9.875 | 0.000 |
| Diabetes (n) | 27 | 8 | 4.621, 2.122-9.407 | 0.000 |
| Coronary heart disease (n) | 9 | 3 | 3.418,1.065-11.003 | 0.020 |

Note: *: BMI=24-27.9 kg/m$^2$.

approved by the Ethics Committee of Jiangxi Provincial People's Hospital. Signed written informed consents were obtained from all participants before the study.

### Deoxyribonucleic Acid (DNA) Extraction and Genotyping

Preparation of DNA samples was as follows: peripheral blood was first subjected to sodium citrate anticoagulation. Genome DNAs were then extracted from the blood according to the instructions of TIANamp Blood DNA Kit (Tiangen, Beijing, China). Following 2% agarose gel electrophoresis, DNA products were stained with ethidium bromide and observed under an ultraviolet lamp. Two SNP sites of MRAS gene were genotyped by the ABI multiplex SNaPshot method (Applied Biosystems, Foster City, CA, USA). Technical support was provided by Shanghai Generay Biotech Co., Ltd. (Shanghai, China). Primer sequences used in our study were shown in Table II.

### Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. Measurement data were presented as ( $\bar{\chi}$±s), and intergroup comparisons were completed using *t*-test. Enumeration data were expressed as frequency, and $\chi^2$-test was performed for intergroup comparisons. The genetic equilibrium was tested by the Hardy-Weinberg equilibrium. All tests were two-sided, with the significance level of α=0.05. $p<0.05$ was considered statistically significant.

## Results

### Distribution Frequencies of Genotypes and Alleles at the two Polymorphic Loci

A total of 135 AS patients and 150 non-AS people were enrolled in this study. It was found that all genotypes at rs9818870 and rs3755751 showed no statistically significant differences between the two groups ($p>0.05$). Meanwhile, their distributions conformed to the Hardy-Weinberg equilibrium law ($p>0.05$) (Table III and IV).

**Table III.** Hardy-Weinberg equilibrium test results of MRAS gene rs9818870 and rs3755751.

| SNP | Frequency | Allele | p |
|---|---|---|---|
| rs9818870 | 0.035 | T | 0.551 |
| rs3755751 | 0.025 | T | 0.487 |

**Table II.** Primer sequences.

| SNP | Forward | Reverse | Extended |
|---|---|---|---|
| rs9818870 | 5'-TCG GTT TCT CAG ATC TGT CTC-3' | 5'-GCT TAT AGA GGT GGT AGT CAG-3' | 5'-TTT TTT TTT GAC GTG TCA GTG TAT TC-3' |
| rs3755751 | 5'-CCT CAA TGA CTT AGA ACC AGC-3' | 5'-TCT ACA GGG TCT TTG GAG CAG-3' | 5'-TTT TTT TTT TTT TTT AGG AAG CCT GCA TGG GATT-3' |

**Table IV.** Distribution frequencies of genotypes.

| Genotype | Observation group (n=135) | | Control group (n=150) | | $\chi^2$ | p |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| rs9818870 | | | | | | |
| CC | 131 | 97.0 | 146 | 97.3 | 0.81 | 0.37 |
| CT | 3 | 2 | 3 | 2 | 0 | 1 |
| TT | 1 | 1 | 1 | 0.7 | 0 | 1 |
| C | 265 | 98.1 | 295 | 98.3 | 1.61 | 0.20 |
| T | 5 | 1.9 | 5 | 1.7 | 0 | 1 |
| rs3755751 | | | | | | |
| CC | 81 | 60 | 79 | 52.7 | 0.03 | 0.87 |
| CT | 47 | 34.8 | 64 | 42.7 | 2.6 | 0.11 |
| TT | 7 | 5.2 | 7 | 4.6 | 0 | 1 |
| C | 209 | 77.4 | 222 | 74 | 0.39 | 0.53 |
| T | 61 | 22.6 | 78 | 26 | 2.1 | 0.15 |

### Analysis of Correlation with MRAS Gene Polymorphism

According to the comparison of AS risk between different models, subjects with genotype TT at rs9818870 exhibited significantly higher risk of AS ($p$=0.041 <0.05), and the differences were statistically significant (Table V).

### Stratified Analysis of Basic Diseases for the Correlation Between rs9818870 and the Onset of AS

The recessive model at rs9818870 (GG+AG/AA) in patients with coronary heart disease in observation group was correlated with AS ($p$=0.048 <0.05) (Table VI).

**Table V.** Analysis of correlations of AS with the two genetic loci.

| Locus | Group | OR (95% CI), p | | | |
|---|---|---|---|---|---|
| | | Additive model | Dominant model | Recessive model | Allele model |
| rs9818870 | Observation group | 1.178 (0.998-1.525) | 1.039 (0.925-1.514) | 1.651 (1.025-2.531) | 1.124 (0.974-1.534) |
| C>T | Control group | $p$=0.071 | $p$=0.071 | $p$=0.041 | $p$=0.065 |
| rs3755751 | Observation group | 1.133 (0.879-1.218) | 1.133 (0.915-1.524) | 1.603 (0.945-2.224) | 1.217 (0.987-1.299) |
| A>G | Control group | $p$=0.128 | $p$=0.281 | $p$=0.085 | $p$=0.103 |

**Table VI.** Stratified analysis of basic diseases for the correlation between rs9818870 and the onset of AS.

| Locus | Stratification | Group | OR (95% CI), p | | |
|---|---|---|---|---|---|
| | | | Additive model | Dominant model | Recessive model |
| rs9818870 | Hypertension | Control group | 1.425 (0.977-1.984) | 1.435 (0.921-2.226) | 1.755 (0.812-3.385) |
| | Non-hypertension | Observation group | $p$=0.061 | $p$=0.098 | $p$=0.152 |
| | Diabetes | Control group | 1.124 (0.868-1.316) | 1.215 (0.784-1.514) | 1.599 (0.842-3.314) |
| | Non-diabetes | Observation group | $p$=0.332 | $p$=0.651 | $p$=0.136 |
| | Coronary heart disease | Control group | 1.107 (0.766-1.341) | 0.952 (0.675-1.342) | 1.246 (0.615-2.336) |
| | Non-coronary heart disease | Observation group | 0.941 | 0.807 | 0.048 |

**Table VII.** Stratified analysis of basic diseases for the correlation between rs3755751 and the onset of AS.

| Locus | Stratification | Group | OR (95% CI), *p* | | |
|---|---|---|---|---|---|
| | | | Additive model | Dominant model | Recessive model |
| rs3755751 | Hypertension | Control group | 1.214 (0.867-1.661) | 1.435 (0.921-2.226) | 1.421 (0.627-3.281) |
| | Non-hypertension | Observation group | p=0.259 | p=0.027 | p=0.374 |
| | Diabetes | Control group | 1.133 (0.884-1.416) | 1.325 (0.873-1.524) | 1.322 (0.813-2.415) |
| | Non-diabetes | Observation group | p=0.288 | p=0.435 | p=0.324 |
| | Coronary heart disease | Control group | 0.964 (0.744-1.271) | 0.952 (0.675-1.312) | 1.135 (0.604-2.214) |
| | Non-coronary heart disease | Observation group | 0.842 | 0.655 | 0.714 |

### *Stratified Analysis of Basic Diseases for the Correlation Between rs3755751 and the Onset of AS*

The dominant model at rs3755751 in hypertension patients in observation group was associated with AS ($p$=0.027 <0.05) (Table VII).

## Discussion

AS is a common disease seriously endangering human health. It refers to endarterial lipid deposition that can gradually form atheros plaques to result in vascular endothelial injury. AS also serves as a major pathological basis of such cardiovascular and cerebrovascular diseases, as coronary heart disease and cerebral embolism. However, its pathogenesis has not yet been fully clarified so far. Currently, the judgment of severity in AS patients still mainly depends on the measurement of arterial cross section, but such a measurement is absolutely not very accurate. In addition to the known early prevention measures, such as controlling blood glucose and pressure and improving diet habit, genetic studies have been started to prevent AS at the genetic level and early diagnosis. This can finally reduce the morbidity rate of AS[6].

Some studies[7] in Europe have found that MRAS is a risk gene causing cardiovascular disease. MRAS, a member in the GTP-binding protein Ras gene family, is located on chromosome 3q22.3. It is highly expressed in the aorta and heart tissues of mice and humans. Acting as a signal transducer, MRAS participates in cell growth and differentiation and promotes the generation of vascular adhesion factors[8-10]. Different adhesion factors interact with immunocytes in the early stage of AS, thereby triggering the migration and aggregation of leucocytes and lymphocytes from the blood to vascular endothelial cells and leading to vascular endothelial cell injury. In this process, adhesion molecules are important factors. Active MRAS has already been observed to be able to effectively induce lymphocyte aggregation. More importantly, evidence[11] has shown that MRAS plays a crucial role in adhesion factor signaling. In recent years, some studies[12,13] have demonstrated that MRAS gene is not only associated with cardiovascular diseases, but also correlated with schizophrenia, hypercholesterolemia, hyperlipidemia, and obesity. van Rooij et al[14] have found that MRAS gene rs9818870 affects cardiomyocyte metabolism. MRAS locus rs9818870, a novel risk gene for CAD, has been discovered through several studies. It is also one of the predictors for cardiovascular diseases[15-18]. A comparative study has also suggested that MRAS rs3755751 has no direct relationship with cerebral stroke in youngsters.

In the present study, there were no statistically significant differences in the frequencies at gene loci rs9818870 and rs3755751 between the two groups ($p$>0.05). Subjects with rs9818870 genotype TT exhibited significantly higher risk of AS ($p$=0.041 <0.05). The recessive model of rs9818870 (GG + AG/AA) in AS patients with coronary heart disease was correlated with AS ($p$=0.048<0.05). Conversely, the dominant model of rs3755751 (TT/TC+CC) in those with hypertension was associated with AS ($p$=0.027<0.05). Our findings revealed that MRAS gene was correlated with the onset of AS to a certain degree. There were still some limitations in the present report. First, the stratified analysis only focused on basic diseases, such as hypertension, coronary heart disease, and diabetes. According to the etiology of AS, sex, age, weight, blood lipid level, and even environmental factors, they might affect the development and progression of AS. However, they

were not statistically analyzed in this study. Second, this investigation had a limited sample size, and human gene types and content varied with environment and race. Therefore, large numbers of samples were required for further research.

## Conclusions

We found that MRAS gene is correlated with the onset of AS. However, further research is needed.

### Conflict of Interests

The authors declare that they have no conflict of interest.

## References


1) Flore R, Zocco MA, Ainora ME, Fonnesu C, Nesci A, Gasbarrini A, Ponziani FR. A novel ultrasound-based vascular calcification score (CALCS) to detect subclinical atherosclerosis. Eur Rev Med Pharmacol Sci 2018; 22: 736-742.
2) Humphries SE, Morgan L. Genetic risk factors for stroke and carotid atherosclerosis: insights into pathophysiology from candidate gene approaches. Lancet Neurol 2004; 3: 227-235.
3) Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, Taubert KA. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. Circulation 2003; 108: 1278-1290.
4) Pasternak RC, Criqui MH, Benjamin EJ, Fowkes FG, Isselbacher EM, McCullough PA, Wolf PA, Zheng ZJ. Atherosclerotic vascular disease conference: writing group I: epidemiology. Circulation 2004; 109: 2605-2612.
5) Erdmann J, Grosshennig A, Braund PS, Konig IR, Hengstenberg C, Hall AS, Linsel-Nitschke P, Kathiresan S, Wright B, Tregouet DA, Cambien F, Bruse P, Aherrahrou Z, Wagner AK, Stark K, Schwartz SM, Salomaa V, Elosua R, Melander O, Voight BF, O'Donnell CJ, Peltonen L, Siscovick DS, Altshuler D, Merlini PA, Peyvandi F, Bernardinelli L, Ardissino D, Schillert A, Blankenberg S, Zeller T, Wild P, Schwarz DF, Tiret L, Perret C, Schreiber S, El MN, Schafer A, Marz W, Renner W, Bugert P, Kluter H, Schrezenmeir J, Rubin D, Ball SG, Balmforth AJ, Wichmann HE, Meitinger T, Fischer M, Meisinger C, Baumert J, Peters A, Ouwehand WH, Deloukas P, Thompson JR, Ziegler A, Samani NJ, Schunkert H. New susceptibility locus for coronary artery disease on chromosome 3q22.3. Nat Genet 2009; 41: 280-282.
6) Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El MN, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013; 45: 25-33.
7) O'Donnell CJ, Kavousi M, Smith AV, Kardia SL, Feitosa MF, Hwang SJ, Sun YV, Province MA, Aspelund T, Dehghan A, Hoffmann U, Bielak LF, Zhang Q, Eiriksdottir G, van Duijn CM, Fox CS, de Andrade M, Kraja AT, Sigurdsson S, Elias-Smale SE, Murabito JM, Launer LJ, van der Lugt A, Kathiresan S, Krestin GP, Herrington DM, Howard TD, Liu Y, Post W, Mitchell BD, O'Connell JR, Shen H, Shuldiner AR, Altshuler D, Elosua R, Salomaa V, Schwartz SM, Siscovick DS, Voight BF, Bis JC, Glazer NL, Psaty BM, Boerwinkle E, Heiss G, Blankenberg S, Zeller T, Wild PS, Schnabel RB, Schillert A, Ziegler A, Munzel TF, White CC, Rotter JI, Nalls M, Oudkerk M, Johnson AD, Newman AB, Uitterlinden AG, Massaro JM, Cunningham J, Harris TB, Hofman A, Peyser PA, Borecki IB, Cupples LA, Gudnason V, Witteman JC. Genome-wide association study for coronary artery calcification with follow-up in myocardial infarction. Circulation 2011; 124: 2855-2864.

8) Gao X, Satoh T, Liao Y, Song C, Hu CD, Kariya KK, Kataoka T. Identification and characterization of RA-GEF-2, a Rap guanine nucleotide exchange factor that serves as a downstream target of M-Ras. J Biol Chem 2001; 276: 42219-42225.

9) Watanabe-Takano H, Takano K, Keduka E, Endo T. M-Ras is activated by bone morphogenetic protein-2 and participates in osteoblastic determination, differentiation, and transdifferentiation. Exp Cell Res 2010; 316: 477-490.

10) Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. Arterioscler Thromb Vasc Biol 2007; 27: 2292-2301.

11) Yoshikawa Y, Satoh T, Tamura T, Wei P, Bilasy SE, Edamatsu H, Aiba A, Katagiri K, Kinashi T, Nakao K, Kataoka T. The M-Ras-RA-GEF-2-Rap1 pathway mediates tumor necrosis factor-alpha dependent regulation of integrin activation in splenocytes. Mol Biol Cell 2007; 18: 2949-2959.

12) Hukic DS, Osby U, Olsson E, Hilding A, Ostenson CG, Gu HF, Ehrenborg E, Edman G, Schalling M, Lavebratt C, Frisen L. Genetic variants of increased waist circumference in psychosis. Psychiatr Genet 2017; 27: 210-218.

13) Alshahid M, Wakil SM, Al-Najai M, Muiya NP, Elhawari S, Gueco D, Andres E, Hagos S, Mazhar N, Meyer BF, Dzimiri N. New susceptibility locus for obesity and dyslipidaemia on chromosome 3q22.3. Hum Genomics 2013; 7: 15.

14) van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, Richardson JA, Olson EN. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proc Natl Acad Sci U S A 2006; 103: 18255-18260.

15) Lu X, Wang L, Chen S, He L, Yang X, Shi Y, Cheng J, Zhang L, Gu CC, Huang J, Wu T, Ma Y, Li J, Cao J, Chen J, Ge D, Fan Z, Li Y, Zhao L, Li H, Zhou X, Chen L, Liu D, Chen J, Duan X, Hao Y, Wang L, Lu F, Liu Z, Yao C, Shen C, Pu X, Yu L, Fang X, Xu L, Mu J, Wu X, Zheng R, Wu N, Zhao Q, Li Y, Liu X, Wang M, Yu D, Hu D, Ji X, Guo D, Sun D, Wang Q, Yang Y, Liu F, Mao Q, Liang X, Ji J, Chen P, Mo X, Li D, Chai G, Tang Y, Li X, Du Z, Liu X, Dou C, Yang Z, Meng Q, Wang D, Wang R, Yang J, Schunkert H, Samani NJ, Kathiresan S, Reilly MP, Erdmann J, Peng X, Wu X, Liu D, Yang Y, Chen R, Qiang B, Gu D. Genome-wide association study in Han Chinese identifies four new susceptibility loci for coronary artery disease. Nat Genet 2012; 44: 890-894.

16) Ellis KL, Frampton CM, Pilbrow AP, Troughton RW, Doughty RN, Whalley GA, Ellis CJ, Skelton L, Thomson J, Yandle TG, Richards AM, Cameron VA. Genomic risk variants at 1p13.3, 1q41, and 3q22.3 are associated with subsequent cardiovascular outcomes in healthy controls and in established coronary artery disease. Circ Cardiovasc Genet 2011; 4: 636-646.

17) Haas U, Sczakiel G, Laufer SD. MicroRNA-mediated regulation of gene expression is affected by disease-associated SNPs within the 3'-UTR via altered RNA structure. RNA Biol 2012; 9: 924-937.

18) Watanabe-Takano H, Takano K, Keduka E, Endo T. M-Ras is activated by bone morphogenetic protein-2 and participates in osteoblastic determination, differentiation, and transdifferentiation. Exp Cell Res 2010; 316: 477-490.