Journal of Biochemistry and Molecular Biology, Vol. 38, No. 2, March 2005, pp. 238-242

JOURNAL OF Biochemistry and Molecular Biology

The Association between the T102C Polymorphism of the HTR2A Serotonin Receptor Gene and HDL Cholesterol Level in Koreans

Jin-Ho Choi[†,‡,$], Shu-Ying Zhang[‡,$], Kyung-Woo Park[‡,||], Young-Seok Cho[‡,||], Byung-Hee Oh[‡,||], Myoung-Mook Lee[‡,||], Young-Bae Park[‡,||] and Hyo-Soo Kim[‡,||,*]

[†]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Kangnam-ku, Seoul 135-710, Korea

[‡]Clinical Research Institute, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea

[||]Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea

Received 25 October 2004, Accepted 22 February 2005

5-HT2A is one of major serotonin receptor that is involved in the action of serotonin-targeting drugs. Previous clinical studies have shown an unexpected association between lower cholesterol level and psychiatric diseases, in which T102C polymorphism of HTR2A, gene of 5-HT2A serotonin receptor, might be involved. Therefore, we hypothesized a potential association between lower cholesterol level and T102C polymorphism. The effect of the T102C polymorphism on the serum lipid profiles of 646 subjects without specific psychiatric disease was investigated. Genotype was determined by polymerase chain reaction and restriction fragment length polymorphism analysis. There were significantly lower levels of total cholesterol (193.6 ± 35.0 *versus* 202.1 ± 45.5 mg/dl, $p = 0.016$) and HDL-cholesterol (42.7 ± 11.6 *versus* 46.3 ± 12.7 mg/dl, $p = 0.004$) in CC genotype than non-CC genotypes. Moreover, multivariate analysis showed that the CC genotype is a strong predictor of a lower HDL-cholesterol level ($p < 0.001$). In conclusion, this study shows that the CC genotype of the HTR2A gene is related to lower HDL-cholesterol level in Koreans. This is the first demonstration showing the potential genetic relationship between the serotonin receptor gene polymorphism and the HDL-cholesterol level.

Keywords: Cholesterol, Genetic polymorphism, Serotonin receptor

Introduction

Despite much evidence that cardiovascular disease outcome can be improved by lipid-lowering therapy (Sacks *et al.*, 1996), there is a remaining concern that lower cholesterol levels may affect mental health (Muldoon *et al.*, 2001). Community cohort studies and meta-analyses of randomized trials have found excess numbers of violent deaths among men receiving cholesterol-lowering therapy (Golomb, 1998), and in large population enrolled in a health screening (Golomb *et al.*, 2000). In addition, the risks of depression (Rozzini *et al.*, 1996) and suicide (Golier *et al.*, 1995; Zureik *et al.*, 1996; Kaplan *et al.*, 1997; Sarchiapone *et al.*, 2001; Kim *et al.*, 2002) have been reported to be associated with low cholesterol levels.

To explain these findings, a hypothesis known as the cholesterol-serotonin hypothesis has been proposed; more specifically, decreased cholesterol levels cause serotonin neurotransmitter system dysfunction, which is linked to a variety of psychological diseases (Engelberg, 1992; Kaplan *et al.*, 1994; Hillbrand *et al.*, 2000).

Of the wide variety of serotonin receptors (Buhot, 1997), the 5-HT2A receptor has become the focus of attention because of the receptor's involvement in the action of atypical antipsychotic drugs (Nocjar *et al.*, 2002). Recently a single nucleotide polymorphism in exon 1 of the 5-HT2A receptor gene (HTR2A), the T102C polymorphism, was identified. The C allele of this polymorphism is known to be related to a variety of psychiatric disease (Du *et al.*, 2000; Arias *et al.*, 2001; Bjork *et al.*, 2002; Levitan *et al.*, 2002; Walitza *et al.*, 2002), suggesting that the T102C polymorphism is related to the function of 5-HT2A receptor.

Both cardiovascular diseases and psychiatric diseases are very important public healthcare issues. Because the suppression of

[$]The first two authors equally contributed to this work.

*To whom correspondence should be addressed.
Tel: 82-2-2072-2226; Fax: 82-2-766-8904
E-mail: hyosoo@snu.ac.kr

cholesterol levels benefits patients that suffer from cardiovascular diseases but may increase psychiatric diseases theoretically, the relationship between cholesterol level and serotonergic activity needs to be clarified. In this case-controlled study, we investigated the association between the HTR2A gene T102C polymorphism and blood cholesterol levels.

Materials and Methods

Subjects Six hundred and forty six study subjects were recruited from inpatients admitted to Seoul National University Hospital Cardiovascular Center for the evaluation of chest pain, from 1997 to 1999. Routine history taking and physical examination were performed by qualified physicians at the outpatient clinic. Patients with a history of psychiatric diseases or mood problems were excluded. After informed consent had been obtained, diagnostic coronary angiography was performed and 10 ml of peripheral blood was drawn for DNA preparation. The diagnosis of coronary artery disease and variant angina was determined in accordance with AHA/ACC guidelines (Scanlon *et al.*, 1999). Clinical parameters were collected and analyzed by independent physicians unaware of the genotyping results. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

Determination of genotypes Genomic DNA was prepared from peripheral blood mononuclear cells using phenol/chloroform extraction and ethanol precipitation. The genotypes were determined by polymerase chain reaction (PCR) and restriction enzyme digestion with *Msp*I endonuclease. We followed previously described protocols (Arranz *et al.*, 1996). Briefly, PCR was performed using the following primers; sense primer 5'- TCT GCT ACA AGT TCT GGC TT -3' and antisense primer 5'- CTG CAG CTT TTT CTC TAG GG -3'. 40 pmol of each primer and 0.5 μg of genomic DNA were mixed with 0.2 mM dNTPs, 1.5 mM $MgCl_2$, and 10 mM 0.2 U of Taq polymerase (Genenmed, Seoul, Korea) in a final volume of 20 μl. The PCR conditions used were; 35 cycles of 60 s at 94°C, 60 s at 58°C, and 60 s at 72°C. PCR products were digested with 1 U of restriction endonuclease *Msp*I (Boehringer-Mannheim, Mannheim, Germany) at 37°C for 2 h. Electrophoresis on 1.6% agarose gel with ethidium bromide allowed the identification of the undigested 342-bp sized PCR product, representing the T allele, and 126-bp and 216-bp sized PCR products, representing the C allele. Results were confirmed by repeating the genotyping of 15% of the DNA samples, randomly selected, by an independent investigator; 100% agreement was obtained.

Statistical methods Categorical variables were evaluated using the χ^2 test, and continuous variables by the Student's t-test. The observed genotype frequencies were compared with the expected under Hardy-Weinberg equilibrium values by χ^2 tests. Mean plasma lipid levels, age, the presence of diabetes, hypertension, and smoking were compared between male and females. The plasma concentrations of lipids were also compared between different genotypes using t-test. An analysis of the covariance was used to test the association between HDL-cholesterol and T102C polymorphism, controlling for age, gender, diabetes, hypertension, smoking, body mass index, and coronary artery disease. All analysis were performed using SPSS for windows version 11.5 (SPSS Inc, Chicago, USA), and statistical significance was accepted when the two-sided *p*-value was less than 0.05.

Results

Study population The baseline characteristics of the patients were summarized in Table 1. Four hundred twenty eight men 218 women were enrolled for the study. Mean age, body mass index (BMI), the presence of diabetes were similar between men and women. There were a significantly higher percentage of smoker and coronary artery disease in men. Mean triglyceride was significantly higher in men than in women. Mean total cholesterol, LDL-cholesterol, and HDL cholesterol were significantly higher in women than in men. There was also a significantly higher percentage of hypertension in women (Table 1).

Table 1. Clinical demographics

	Men	Women	p-value
Number	428	218	-
Age (year)	55.4±10.2	56.3±8.7	0.252
Diabetes (%)	19.6 (84)	24.8 (54)	0.155
Hypertension (%)	36.0 (154)	48.2 (105)	0.003*
Smoker (%)	42.1 (180)	6.0 (13)	<0.001*
BMI (kg/M^2)	24.5±2.7	24.7±3.4	0.627
Total cholesterol (mg/dL)	196.6±10.2	206.1±50.6	0.010*
LDL-cholesterol (mg/dL)	123.7±35.3	132.9±49.4	0.013*
HDL-cholesterol (mg/dL)	43.8±11.5	48.5±13.8	< 0.001*
Triglyceride (mg/dL)	141.6±64.4	125.1±70.1	0.006*
Coronary artery disease (%)	45.6 (195)	35.8 (78)	0.019*

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein. The actual number of patients is shown in parenthesis. There were significant differences between men and women for total cholesterol, LDL-cholesterol, HDL-cholesterol, the percentage of hypertension, smoker, and coronary artery disease (*p<0.05).

Table 2. Genotype distribution and allele frequency in men and women

Genotype and Allele	Men	Women
CC	24.3% (104)	27.5% (60)
CT	52.1% (223)	50.5% (110)
TT	23.6% (101)	22.0% (48)
C	0.503	0.527
T	0.497	0.473

The numbers in parenthesis are the actual number of patients. The distribution of the genotypes was compatible with the Hardy-Weinberg equilibrium, and similar between men and women.

Allele frequency and genotype distribution of the T102C polymorphism and its relationship with clinical characteristics and lipid levels The distribution of CC : CT : TT genotypes in men and women were 24.3 : 52.1 : 23.6% and 27.5 : 50.5 : 22.0%, giving a C allele frequency of 0.497 for men and 0.473 for women. These findings were consistent with Hardy Weinberg expectations (Table 2).

When the genotype distribution was analyzed according to the clinical characteristics including age, diabetes, hypertension, smoking, body mass index (BMI), coronary artery disease (CAD), we found no significant associations between the T102C polymorphism and these clinical characteristics. There were also no associations between the genotypes and LDL-cholesterol and triglyceride. However, we discovered that total cholesterol and HDL-cholesterol were significantly lower in the CC genotype when compared to the non-CC genotype (total cholesterol, 193.6 ± 35.0 versus 202.1 ± 45.5 mg/dL, $p = 0.016$; HDL-cholesterol, 42.7 ± 11.6 versus 46.3 ± 12.7 mg/dL, $p = 0.004$) (Table 3).

Next we analyzed men and women separately, because the lipid levels were significantly different between men and women. There was still no association between the polymorphism and clinical characteristics even the genotype distribution was analyzed separately in men and women (data not shown). However, the association between HDL-cholesterol and the genotypes were significant both in men (44.5 ± 11.4 versus 41.6 ± 11.3 mg/dL, $p = 0.038$) and women (49.9 ± 14.2 versus 44.7 ± 12.1 mg/dL, $p = 0.023$). The association between total cholesterol and the genotypes were no longer significant in men (198.3 ± 38.6 versus 191.6 ± 37.5 mg/dL, $p = 0.126$), while the association in women remained significant (209.5 ± 56.2 versus 197.1 ± 29.8 mg/dL, $p = 0.042$) (Table 4).

Because the levels of LDL-cholesterol, a major non-HDL-cholesterol, and triglyceride were not significantly different between genotypes, the difference of HDL-cholesterol between genotypes might lead to the difference of total cholesterol between genotypes. So the effect of CC genotype on HDL-cholesterol might explain our data. Therefore, we analyzed the effect of CC genotype on HDL-cholesterol. Univariate analysis for age, hypertension, sex, diabetes, smoking, body mass index, and coronary artery disease revealed no single factor that was significantly related to the HDL-cholesterol level. To exclude the effects of other factors, which might confound the relationship between T102C polymorphism and HDL-cholesterol, an analysis of covariance (ANCOVA) that controlled for age, hypertension, sex, diabetes, smoking, body mass index, and coronary artery disease was performed. The CC genotype was significantly associated with HDL-cholesterol levels ($p<0.001$), and explained the 7.9% variance in the HDL-cholesterol levels.

Discussion

Our study shows that a common polymorphism of the

Table 3. Risk factors and genotypes

	CC	Non-CC	p-value
Distribution (%)	25.4 (164)	74.6 (482)	-
Age (year)	56.3 ± 9.9	55.5 ± 9.7	0.376
Diabetes (%)	21.3 (35)	21.4 (103)	1.000
Hypertension (%)	42.1 (69)	39.4 (190)	0.580
Smoker (%)	31.7 (52)	29.3 (141)	0.555
BMI (kg/M^2)	24.4 ± 3.1	24.6 ± 2.9	0.517
Coronary artery disease (%)	45.7 (75)	41.1 (198)	0.315
Total cholesterol (mg/dL)	193.6 ± 35.0	202.1 ± 45.5	0.016*
LDL-cholesterol (mg/dL)	124.2 ± 30.5	127.7 ± 43.9	0.299
HDL-cholesterol (mg/dL)	42.7 ± 11.6	46.3 ± 12.7	0.004*
Triglyceride (mg/dL)	137.7 ± 64.2	130.8 ± 73.9	0.326

The numbers in parenthesis are the actual number of patients. There was no association between T102C polymorphism and clinical characteristics. However, total cholesterol and HDL-cholesterol were significantly lower in the CC genotype when compared to the non-CC genotype. *: $p<0.05$: CC versus non-CC genotypes.

Table 4. Lipid profiles according to genotype

	Total		Men		Women	
	CC	Non-CC	CC	Non-CC	CC	Non-CC
Number	164	482	104	324	60	158
Total cholesterol	193.6 ± 35.0	202.1 ± 45.5 (*0.016)	198.3 ± 38.6	191.6 ± 37.5 (0.126)	209.5 ± 56.2	197.1 ± 29.8 (*0.042)
LDL-cholesterol	124.2 ± 30.5	127.7 ± 43.9 (0.299)	124.3 ± 36.5	121.8 ± 31.4 (0.549)	134.6 ± 55.2	128.3 ± 28.7 (0.316)
HDL-cholesterol	42.7 ± 11.6	46.3 ± 12.7 (*0.004)	44.5 ± 11.4	41.6 ± 11.3 (*0.038)	49.9 ± 14.2	44.7 ± 12.1 (*0.023)
Triglyceride	137.7 ± 64.2	130.8 ± 73.9 (0.326)	143.5 ± 61.7	135.9 ± 71.9 (0.371)	126.4 ± 67.6	121.8 ± 77.1 (0.710)

Lipid levels given as mean±standard deviation (mg/dL). When men and women are analyzed separately, there were no differences in total cholesterol levels in men. However, the levels of HDL-cholesterol were significantly lower in CC genotype both in men and women, respectively. *: $p<0.05$: CC versus non-CC genotypes.

HTR2A serotonin receptor gene is associated with significantly lower HDL-cholesterol level. Our study excluded all patients on, or with a history of, lipid lowering therapy; thereby, excluding the possibility of lipid level modulation by lipid-lowering therapy. Also, there were no women on hormone replacement therapy. This association is independent of other clinical variables that potentially affect blood lipid levels.

To our knowledge, we identified the T102C polymorphism of HTR2A gene in Koreans for the first time. The frequency of C allele of HTR2A gene of Koreans (0.512) was similar to those of Japanese (0.46) and less common than those of Caucasians (0.69). Our data support previous reports on the variability of the HTR2A gene polymorphism in difference races (Bondy *et al.*, 2000; Yu *et al.*, 2004). Whether the difference in the HDL-cholesterol level between difference races can be explained by the difference in T102C polymorphism is a much more complex issue, and extends beyond the scope of this article. However, along with data from previous studies on Caucasian and Japanese, our study shows that a different T102C polymorphism may partially contribute to the ethnic difference in the HDL-cholesterol level.

Controversy exists on whether T102C polymorphism is functional mutation, because it is a silent mutation, does not change the polypeptide sequence coded by the gene. However, The T102C polymorphism is known to be related to a variety of psychiatric disease (Du *et al.*, 2000; Arias *et al.*, 2001; Bjork *et al.*, 2002; Levitan *et al.*, 2002; Walitza *et al.*, 2002), and clinical studies including meta-analysis revealed that it is also related to the clinical responses to the two 5-HT2A receptor antagonists, clozapine and risperidone (Arranz *et al.*, 1995; Arranz *et al.*, 1998; Lane *et al.*, 2002). Furthermore, pathological study identified that HTR2A mRNA expression is decreased in the human brain cortex in C allele group (Polesskaya *et al.*, 2002). A recently published clinical study found that a lower HDL-cholesterol level is related to altered neuronal serotonergic activity (Buydens-Branchey *et al.*, 2000). These findings support our hypothesis that T102C polymorphism is functional and is related to lower cholesterol levels.

The major limitation of our study was that the results of our study may not be applicable to the general population, because the majority of our study subjects were coronary artery disease patients with heterogeneous diagnosis. However, no difference was observed in the distribution of genotype frequencies between the diagnosis groups, including the normal coronary angiography group.

In conclusion, our study shows that the CC genotype of the T102C polymorphism is significantly associated with a lower level of HDL-cholesterol in Korean. This is the first demonstration showing the potential relationship between the genetic polymorphism of serotonin receptor and the cholesterol levels. Our study also shows that Koreans, when compared to Caucasians, have a lower frequency of C allele of HT2RA T102C polymorphism, which demonstrates the frequency variation among different ethnic groups. In view of the importance of HDL-cholesterol in the public health, these suggested associations of HT2RA T102C polymorphism should be studied further in a larger population of patients.

Acknowledgment This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, and Republic of Korea (0412-CR02-0704-0001). Dr. Hyo-Soo Kim is an investigator of the aging and apoptosis research center at Seoul National University supported by Korea Science and Engineering Foundation (KOSEF).

References

Arias, B., Gutierrez, B., Pintor, L., Gasto, C. and Fananas L. (2001) Variability in the 5-HT(2A) receptor gene is associated with seasonal pattern in major depression. *Mol. Psychiatry* **6**, 239-242.

Arranz, M., Collier, D., Sodhi, M., Ball, D., Roberts, G., Price, J., Sham, P. and Kerwin, R. (1995) Association between clozapine response and allelic variation in 5-HT2A receptor gene. *Lancet.* **346**, 281-282.

Arranz, M. J., Lin, M. W., Powell, J., Kerwin, R. and Collier, D. (1996) 5HT 2a receptor T102C polymorphism and schizophrenia. *Lancet.* **347**, 1831-1832.

Arranz, M. J., Munro, J., Sham, P., Kirov, G., Murray, R. M., Collier, D. A. and Kerwin, R. W. (1998) Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. *Schizophr. Res.* **32**, 93-99.

Bjork, J. M., Moeller, F. G., Dougherty, D. M., Swann, A. C., Machado, M. A. and Hanis, C. L. (2002) Serotonin 2a receptor T102C polymorphism and impaired impulse control. *Am. J. Med. Genet.* **114**, 336-339.

Bondy, B., Kuznik, J., Baghai, T., Schule, C., Zwanzger, P., Minov, C., de Jonge, S., Rupprecht, R., Meyer, H., Engel, R. R., Eisenmenger, W. and Ackenheil, M. (2000) Lack of association of serotonin-2A receptor gene polymorphism (T102C) with suicidal ideation and suicide. *Am. J. Med. Genet.* **96**, 831-835.

Buhot, M. C. (1997) Serotonin receptors in cognitive behaviors. *Curr. Opin. Neurobiol.* **7**, 243-254.

Buydens-Branchey, L., Branchey, M., Hudson, J. and Fergeson, P. (2000) Low HDL cholesterol, aggression and altered central serotonergic activity. *Psychiatry Res.* **93**, 93-102.

Du, L., Bakish, D., Lapierre, Y. D., Ravindran, A. V. and Hrdina, P. D. (2000) Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. *Am. J. Med. Genet.* **96**, 56-60.

Engelberg, H. (1992) Low serum cholesterol and suicide. *Lancet* **339**, 727-729.

Golier, J. A., Marzuk, P. M., Leon, A. C., Weiner, C. and Tardiff, K. (1995) Low serum cholesterol level and attempted suicide. *Am. J. Psychiatry* **152**, 419-423.

Golomb, B. A. (1998) Cholesterol and violence: is there a connection? *Ann. Intern. Med.* **128**, 478-487.

Golomb, B. A., Stattin, H. and Mednick, S. (2000) Low cholesterol and violent crime. *J. Psychiatr. Res.* **34**, 301-309.

Hillbrand, M., Waite, B. M., Miller, D. S., Spitz, R. T. and Lingswiler, V. M. (2000) Serum cholesterol concentrations and mood states in violent psychiatric patients: an experience sampling study. *J. Behav. Med.* **23**, 519-529.

Kaplan, J. R., Muldoon, M. F., Manuck, S. B. and Mann, J. J. (1997) Assessing the observed relationship between low cholesterol and violence-related mortality. Implications for suicide risk. *Ann. N. Y. Acad. Sci.* **836**, 57-80.

Kaplan, J. R., Shively, C. A., Fontenot, M. B., Morgan, T. M., Howell, S. M., Manuck, S. B., Muldoon, M. F. and Mann, J. J. (1994) Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom. Med.* **56**, 479-484.

Kim, Y. K., Lee, H. J., Kim, J. Y., Yoon, D. K., Choi, S. H. and Lee, M. S. (2002) Low serum cholesterol is correlated to suicidality in a Korean sample. *Acta. Psychiatr. Scand.* **105**, 141-148.

Lane, H. Y., Chang, Y. C., Chiu, C. C., Chen, M. L., Hsieh, M. H. and Chang, W. H. (2002) Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. *Am. J. Psychiatry* **159**, 1593-1595.

Levitan, R. D., Masellis, M., Basile, V. S., Lam, R. W., Jain, U., Kaplan, A. S., Kennedy, S. H., Siegel, G., Walker, M. L., Vaccarino, F. J. and Kennedy, J. L. (2002) Polymorphism of the serotonin-2A receptor gene (HTR2A) associated with childhood attention deficit hyperactivity disorder (ADHD) in adult women with seasonal affective disorder. *J. Affect. Disord.* **71**, 229-233.

Muldoon, M. F., Manuck, S. B., Mendelsohn, A. B., Kaplan, J. R. and Belle, S. H. (2001) Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials. *Bmj* **322**, 11-15.

Nocjar, C., Roth, B. L. and Pehek, E. A. (2002) Localization of 5-HT(2A) receptors on dopamine cells in subnuclei of the midbrain A10 cell group. *Neuroscience* **111**, 163-176.

Polesskaya, O. O. and Sokolov, B. P. (2002) Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *J. Neurosci. Res.* **67**, 812-822.

Rozzini, R., Bertozzi, B., Barbisoni, P. and Trabucchi, M. (1996) Low serum cholesterol and serotonin metabolism. Risk of depression is higher in elderly patients with lowest serum cholesterol values. *Bmj* **312**, 1298-1299.

Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D., Cole, T. G., Brown, L., Warnica, J. W., Arnold, J. M., Wun, C. C., Davis, B. R. and Braunwald, E. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N. Engl. J. Med.* **335**, 1001-1009.

Sarchiapone, M., Camardese, G., Roy, A., Della Casa, S., Satta, M. A., Gonzalez, B., Berman, J. and De Risio, S. (2001) Cholesterol and serotonin indices in depressed and suicidal patients. *J. Affect. Disord.* **62**, 217-219.

Scanlon, P. J., Faxon, D. P., Audet, A. M., Carabello, B., Dehmer, G. J., Eagle, K. A., Legako, R. D., Leon, D. F., Murray, J. A., Nissen, S. E., Pepine, C. J., Watson, R. M., Ritchie, J. L., Gibbons, R. J., Cheitlin, M. D., Gardner, T. J., Garson, A., Jr., Russell, R. O. Jr., Ryan, T. J. and Smith, S. C. (1999) ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation* **99**, 2345-2357.

Walitza, S., Wewetzer, C., Warnke, A., Gerlach, M., Geller, F., Gerber, G., Gorg, T., Herpertz-Dahlmann, B., Schulz, E., Remschmidt, H., Hebebrand, J. and Hinney, A. (2002) 5-HT(2A) promoter polymorphism -1438G/A in children and adolescents with obsessive-compulsive disorders. *Mol Psychiatry* **7**, 1054-1057.

Yu, B. N., Wang, A., Zhou, G., Zhang, W., Hu, D. L., Li, Q., He, Y. J. and Zhou, H. H. (2004) T102C genetic polymorphism of the 5-HT2A receptor in Chinese hypertensive patients and healthy controls. *Clin. Exp. Pharmacol. Physiol.* **31**, 847-849.

Zureik, M., Courbon, D. and Ducimetiere, P. (1996) Serum cholesterol concentration and death from suicide in men: Paris prospective study I. *Bmj* **313**, 649-651.