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Original Research Article

Implications of statin metabolism-related gene testing in guiding individualized drug use in cardiovascular diseases

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Abstract

Purpose: *To determine the value of statin metabolism-related gene testing in guiding individualized drug use in cardiovascular and cerebrovascular diseases.*
Methodology: *A total of 158 eligible patients with cardiovascular and cerebrovascular diseases in the Outpatient Department, Yantai City Yantaishan Hospital, Laishan District, Shandong Province were recruited and assigned based on their diseases to group A (81 patients with coronary heart disease), group B (77 patients with cerebral infarction). The control group comprised 75 healthy individuals.*
Results: *The GG, GT, and TT genotypes in ABCB1 (2677G > T) in group A had a G allele frequency of 0.556 and a T allele frequency of 0.444, while CC, CT, and TT genotypes in ABCB1 (3435C > T) in group A had a C allele frequency of 0.555 and a T allele frequency of 0.445. Significant differences were observed in the effectiveness of statins in treating patients with different genotypes ($p < 0.05$).*
Conclusion: *Genetic testing related to statin metabolism is of significant value in guiding the use of medication in patients with cardiovascular disease, as most of these patients present with dyslipidaemia. Significant individual differences in gene polymorphisms exist between patients with the same disease.*

Keywords: *Statins, Metabolism-related gene testing, Cardiovascular diseases, Individualized medication guidance, Value analysis*

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INTRODUCTION

In recent years, the prevalence of dyslipidaemic conditions has increased due to changes in daily habits and diets [1]. Dyslipidemia is one of the causative factors of cardiovascular diseases [2]. The incidence of cardiovascular and cerebrovascular diseases in China is on the increase, with a higher prevalence in the younger population [3].

Dyslipidemia is commonly managed using statins in the clinical setting and results in excellent outcomes [4]. Nonetheless, the individual differences among patients lead to limitations in its generalizability [5]. With the advent of the concept of clinical precision medicine in recent years, metabolism-related genetic testing of statins in the management of dyslipidemia has attracted extensive clinical interest [6].

To this end, three SNP loci of statin metabolism-associated genes {ABCB1 (2677G > T), ABCB1 (3435C > T), SLCO1B1*5 (T > C)} were investigated in this study to guide individualized drug use in cardiovascular diseases.

METHODS

Study population

A total of 158 patients with cardiovascular and cerebrovascular diseases in Yantai City Yantaishan Hospital were recruited and assigned by their diseases to group A (81 patients with coronary heart disease), and group B (77 patients with cerebral infarction). The control group comprised 75 healthy individuals. Approval for the study was received from the institutional ethics committee, and the study complied with the guidelines for human studies.

Inclusion and exclusion criteria

Patients with diagnosis confirmed by clinically relevant test results, with complete clinical data confirming cardiovascular and cerebrovascular diseases, and who provided written informed consent were recruited. Patients with oncological diseases, serious organ diseases, systemic diseases, and poor compliance with therapy were excluded from the study.

Evaluation of lipid-related indices

Venous blood (5 mL) was collected from all participants and centrifuged to obtain the serum. The serum concentrations of total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were determined.

Genetic testing

Elbow venous blood (2 mL) was obtained from each patient and placed in ethylenediamine tetraacetic acid anticoagulation tubes. The blood specimens were pretreated with NH_4Cl to obtain leukocytes. The SNP typing of ABCB1 (2677G > T), ABCB1 (3435C > T), and SLCO1B1*5 (T > C) was done using a fluorescence detector and fluorescent staining hybridization [7].

Statin administration

Forty-five patients in group A receiving statins were treated with 20 mg of atorvastatin (Beijing Jialin Pharmaceutical Co. Ltd, H20093819) daily for 30 days.

Statistical analysis

Data analyses were performed with IBM SPSS statistics 24.0 and Stata 16. The numerical variables are described as means, median, standard deviations (SD), and ranges. Categorical variables are described as frequencies, and inter-group differences were analyzed by chi-square test. Continuous variables with normality were checked with the Kolmogorov–Smirnov test. Inter-group comparison of normally distributed variables was done using *t*-test; non-normal distributed variables were compared using Mann–Whitney *U*-test. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

There were 46 male and 35 female patients in group A, aged 50 - 78 (69.42 ± 11.37) years. They had a mean TC of 4.72 ± 1.43 mmol/L, a mean TG of 3.06 ± 2.45 mmol/L, a mean LDL-C-C of 3.12 ± 1.71 mmol/L, and a mean HDL-C-C of 0.94 ± 0.23 mmol/L. There were 44 male and 33 female patients in group B, aged 48 - 79 (69.39 ± 11.45) years. They had a mean TC of 4.36 ± 0.94 mmol/L, a mean TG of 2.32 ± 1.31 mmol/L, a mean LDL-C-C of 2.64 ± 0.82 mmol/L, and a mean HDL-C-C of 1.10 ± 0.37 mmol/L. There were 43 male and 32 female participants in the control group, aged 49 - 77 (69.37 ± 11.62) years. They had a mean TC of 4.48 ± 0.91 mmol/L, a mean TG of 1.46 ± 0.85 mmol/L, a mean LDL-C-C of 2.83 ± 0.82 mmol/L, and a mean HDL-C-C of 1.24 ± 0.33 mmol/L. Patients in groups A and B exhibited higher TG levels and LDL-C-C levels and lower HDL-C-C levels than the controls ($p < 0.05$) (Table 1).

Genotype distribution and allele frequencies

The GG, GT, and TT genotypes in ABCB1 (2677G > T) in group A were 28, 34, and 19 cases, respectively, with a G allele frequency of 0.556 and a T allele frequency of 0.444; The CC, CT, and TT genotypes in ABCB1 (3435C > T) in group A were 26, 38, and 17 cases, respectively, with a C allele frequency of 0.555 and a T allele frequency of 0.445; The TT, TC, and CC genotypes in SLCO1B1*5 (T > C) in group A were 61, 20, and 0 cases, respectively, with T allele frequency of 0.875 and C allele frequency of 0.125.

Table 1: Patients' baseline data

Parameter	Group A (n=81)	Group B (n=77)	Control group (n=75)
Gender			
Male	46	44	43
Female	35	33	32
Age (year)	69.42±11.37	69.39±11.45	69.37±11.62
TC(mmol/L)	4.72±1.43	4.36±0.94	4.48±0.91
TG(mmol/L)	3.06±2.45*	2.32±1.31*	1.46±0.85
LDL-C-C(mmol/L)	3.12±1.71*	2.64±0.82	2.83±0.82
HDL-C-C(mmol/L)	0.94±0.23*	1.10±0.37*	1.24±0.33

Note: *$P < 0.05$ when compared with the control group

The GG, GT, and TT genotypes in ABCB1(2677G > T) in group B were 26, 27, and 24 cases, respectively, with a G allele frequency of 0.505 and T allele frequency of 0.495; the CC, CT, and TT genotypes in ABCB1(3435C > T) in group B were 28, 35, and 14 cases, respectively, with C allele frequency of 0.588 and T allele frequency of 0.412; the TT, TC, and CC genotypes in SLCO1B1*5 (T > C) in group B were 54, 23, and 0 cases, respectively, with a T allele frequency of 0.849 and a C allele frequency of 0.151 (Table 2).

Lipid-related indices before and after statin treatment

Patients exhibited significantly reduced serum concentrations of TG, TC, and LDL-C and elevated serum concentrations of HDL-C after the administration of statins (all $p < 0.05$) (Table 3).

Lipid-related indices before and after statin treatment

Significant differences were observed in the effectiveness of statins in treating patients with different genotypes ($p < 0.05$) (Table 4).

DISCUSSION

Cardiovascular diseases refer to the development of ischemic or hemorrhagic diseases of the heart and brain caused by hyperlipidemia, hypertension, and atherosclerosis [8]. Studies suggested that dyslipidemia is a major contributor to the occurrence and development of cardiovascular and cerebrovascular diseases [9]. Therefore, lipid control in patients with dyslipidemia is the main preventive and curative measure in clinical practice. Several studies have confirmed that alterations in human lipid metabolism, especially elevated serum LDL-C concentrations and decreased serum HDL-C concentration contribute to increased morbidity and mortality of cardiovascular and cerebrovascular diseases [10]. The present study suggests a negative and exclusive correlation between HDL-C and the occurrence of cardiovascular disease and significant differences in lipid levels between patients with cardiovascular disease and the healthy population.

Table 2: Genotype distribution and allele frequencies

Parameter	Group A (n=81)	Group B (n=77)
ABCB1(2677G＞T)		
GG	28	26
GT	34	27
TT	19	24
G allele frequency	0.556	0.505
T allele frequency	0.444	0.495
ABCB1(3435C＞T)		
CC	26	28
CT	38	35
TT	17	14
C allele frequency	0.555	0.588
T allele frequency	0.445	0.412
SLCO1B1*5(T＞C)		
TT	61	54
TC	20	23
CC	0	0
G allele frequency	0.875	0.849
T allele frequency	0.125	0.151

Table 3: Comparison of lipid-related indicators before and after statin treatment

Parameter	TC (mmol/L)	TG (mmol/L)	LDL-C-C (mmol/L)	HDL-C-C (mmol/L)
Before treatment	4.92±1.63	2.57±0.83	3.14±1.35	0.95±0.23
After treatment	3.72±1.09	1.26±0.34	1.94±0.87	1.12±0.20
T	4.105	9.797	5.012	-3.742
P-value	＜0.001	＜0.001	＜0.001	＜0.001

Table 4: Comparison of lipid-related indicators before and after statin treatment in patients with different genotypes

Parameter	n	**TC** (mmol/L)	**TG** (mmol/L)	**LDL-C-C** (mmol/L)	**HDL-C-C** (mmol/L)
ABCB1(2677G＞T)	***45***				
GG	*12*				
Before treatment		4.87±1.52	2.55±0.78	1.31±0.38	1.02±0.27
After treatment		3.67±1.19*	1.09±0.23*	2.07±1.22*	1.05±0.17
GT	*22*				
Before treatment		4.95±1.92	3.11±0.54	3.13±1.58	0.88±0.19
After treatment		3.61±1.22*	1.17±0.32*	1.92±0.85*	1.11±0.20
TT	*11*				
Before treatment		4.84±1.31	1.93±0.89	2.84±1.06	0.95±0.32
After treatment		3.88±0.86	1.19±0.67*	1.91±0.67	1.16±0.31
ABCB1(3435C＞T)	***45***				
CC	*11*				
Before treatment		5.41±1.72	1.91±0.78	3.07±1.73	0.97±0.22
After treatment		4.13±1.45*	1.69±0.39*	2.04±0.95*	1.08±0.26
CT	*26*				
Before treatment		4.83±1.69	1.47±0.52	3.19±1.41	0.93±0.26
After treatment		3.57±1.06*	1.02±0.44*	1.94±0.95*	1.12±0.22*
TT	*8*				
Before treatment		4.41±1.47	1.28±0.68	2.97±0.85	0.88±0.14
After treatment		3.56±0.61	1.11±0.19	1.86±0.62*	1.09±0.18*
SLCO1B1*5(T＞C)	***45***				
TT	*36*				
Before treatment		4.77±1.63	1.64±0.52	3.07±1.32	0.93±0.25
After treatment		3.72±1.10*	1.16±0.39*	1.95±0.86*	1.10±0.23*
TC	*9*				
Before treatment		5.41±1.62	2.35±1.06	3.39±1.78	0.90±0.24
After treatment		3.71±1.22*	1.04±0.69*	1.92±0.91*	1.15±0.25*

Note: *$P < 0.05$ when compared with pre-treatment data

Statins are currently the preferred option for the management of dyslipidemic conditions [11]. Evidence suggests that statins play a key role in reducing TC, TG, and LDL-C levels, and elevating HDL-C levels [12]. However, they are associated with liver dysfunction and rhabdomyolysis due to individual differences among patients [13].

It has been found that the main cause of individual differences triggered by statins is genetic after excluding the influencing factors such as gender and age [14]. Genomic testing of statins prior to treatment is, therefore, imperative [15], as it predicts the risk of statin use, and evaluates the efficacy of statins, thereby providing medication guidance for patients [16].

The present study showed significantly reduced TG, TC, and LDL-C levels and increased HDL-C levels after the administration of statins, confirming the effectiveness of statins in regulating blood lipids. To further clarify the differences in response to statins across genotypes, changes in lipid levels in 45 patients with different genetic polymorphisms before and after treatment were compared. The ABCB1 gene encodes a product of the intestinal efflux transporter P-glycoprotein, which reduces drug absorption and limits drug utilization [17]. Evidence suggested that GG patients with ABCB1 (2677G > T) type GG exhibited significantly better improvement in TC and HDL-C levels on statins than non-GG patients. In the present study, the efficacy of statins was significantly stronger in GT patients than in non-GT patients, which is inconsistent with the findings of Ruiz-Iruela et al [18].

This inconsistency indicates that the effects of genetic polymorphisms on ABCB1 transport and statins still require further investigation. It has been found that among 3435C > T, patients with CC and CT types who took statins had significantly better HDL-C elevation and LDL-C reduction than those with TT types, which were consistent with the findings in the current study. These results indicate that among 3435C > T, the lipid-lowering effect is more desirable in patients with CT type. SLCO1B1*5 (T > C) is the risk gene for determining statins [19], where TT type is normally metabolized, and its metabolism of statins is normal. The CT type is intermediate in metabolism and is less able to metabolize statins. Patients with CC type have an extremely weak response to statins, and the weaker metabolism means that patients are at higher risk of adverse reactions from statins. The results of

the current study showed that the lipid-lowering effect in SLCO1B1*5 (T > C) was better in TT patients than in non-TT patients, which is similar to the results of previous studies [20].

CONCLUSION

Genetic testing with regard to statin metabolism is of high value in guiding the use of medication in patients with cardiovascular disease, as most of these patients present with dyslipidemia. Significant individual differences in gene polymorphisms exist between patients with the same disease. This procedure can be further investigated as a tool for guidance in selecting medication choices for various disease conditions.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Yantai City Yantaishan Hospital.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Singh S, Bittner V. Familial hypercholesterolemia-epidemiology, diagnosis, and screening. Curr Atheroscler Rep 2015; 17(2): 482.*
2. *Ballantyne CM, Banach M, Bays HE, Catapano AL, Laufs U, Stroes ESG, Robinson P, Lei L, Ray KK. Long-term safety and efficacy of bempedoic acid in patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). Am J Cardiol 2022; 174: 1-11.*
3. *Guan ZW, Wu KR, Li R, Yin Y, Li XL, Zhang SF, Li Y. Pharmacogenetics of statins treatment: Efficacy and safety. J Clin Pharm Ther 2019; 44(6): 858-867.*
4. *Sirtori CR. The pharmacology of statins. Pharmacol Res 2014; 88: 3-11.*
5. *Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol 2020; 16(9): 809-822.*
6. *Kazi DS, Penko JM, Bibbins-Domingo K. Statins for primary prevention of cardiovascular disease: review of evidence and recommendations for clinical practice. Med Clin North Am 2017; 101(4): 689-699.*
7. *Duarte JD, Cavallari LH. Pharmacogenetics to guide cardiovascular drug therapy. Nat Rev Cardiol 2021; 18(9): 649-665.*
8. *Zhang Q, Dong J, Yu Z. Pleiotropic use of statins as non-lipid-lowering drugs. Int J Biol Sci 2020; 16(14): 2704-2711.*
9. *Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2017; 48(2): e44-e71.*
10. *Marini S, Merino J, Montgomery BE, Malik R, Sudlow CL, Dichgans M, Florez JC, Rosand J, Gill D, Anderson CD. International Stroke Genetics Consortium. Mendelian randomization study of obesity and cerebrovascular disease. Ann Neurol 2020; 87(4): 516-524.*
11. *Bianconi V, Sahebkar A, Banach M, Pirro M. Statins, haemostatic factors and thrombotic risk. Curr Opin Cardiol 2017; 32(4): 460-466.*
12. *Mohammadkhani N, Gharbi S, Rajani HF, Farzaneh A, Mahjoob G, Hoseinsalari A, Korsching E. Statins: Complex outcomes but increasingly helpful treatment*

options for patients. Eur J Pharmacol 2019; 863: 172704.

13. *Ricci G, Ciccone MM, Giordano P, Cortese F. Statins: Pharmacokinetics, pharmacodynamics and cost-effectiveness analysis. Curr Vasc Pharmacol 2019; 17(3): 213-221.*
14. *Rumyantsev NA, Kukes VG, Kazakov RE, Rumyantsev AA, Sychev DA. Ispol'zovanie farmakogeneticheskogo testirovaniia dlia predotvrashcheniia nezhelatel'nykh lekarstvennykh reaktsiĭ pri terapii statinami [Use of pharmacogenetic testing to prevent adverse drug reactions during statin therapy]. Ter Arkh 2017; 89(1): 82-87.*
15. *Srisawasdi P, Rodcharoen P, Vanavanan S, Chittamma A, Sukasem C, Na Nakorn C, Dejthevaporn C, Kroll MH. Association of CETP gene variants with atherogenic dyslipidemia among thai patients treated with statin. Pharmgenomics Pers Med 2021; 14: 1-13.*
16. *Jarmul J, Pletcher MJ, Hassmiller Lich K, Wheeler SB, Weinberger M, Avery CL, Jonas DE, Earnshaw S, Pignone M. Cardiovascular genetic risk testing for targeting statin therapy in the primary prevention of atherosclerotic cardiovascular disease: A cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes 2018; 11(4): e004171.*
17. *van der Baan FH, Knol MJ, Maitland-van der Zee AH, Regieli JJ, van Iperen EP, Egberts AC, Klungel OH, Grobbee DE, Jukema JW. Added value of pharmacogenetic testing in predicting statin response: results from the REGRESS trial. Pharmacogenomics J 2013; 13(4): 318-324.*
18. *Ruiz-Iruela C, Padró-Miquel A, Pintó-Sala X, Baena-Díez N, Caixàs-Pedragós A, Güell-Miró R, Navarro-Badal R, Jusmet-Miguel X, Calmarza P, Puzo-Foncilla JL, et al. KIF6 gene as a pharmacogenetic marker for lipid-lowering effect in statin treatment. PLoS One 2018; 13(10): e0205430.*
19. *Bitto A, Pallio G, Messina S, Arcoraci V, Pizzino G, Russo GT, Pallio S, Squadrito F, Altavilla D. Genomic variations affecting biological effects of statins. Curr Drug Metab 2016; 17(6): 566-572.*
20. *Sadee W. Gene-gene-environment interactions between drugs, transporters, receptors, and metabolizing enzymes: Statins, SLCO1B1, and CYP3A4 as an example. J Pharm Sci 2013; 102(9): 2924-2929.*
21. *Renyong L, Ting X, Qiaoling C, Hongtao L, Le Z. Traditional Chinese medicine combined with conventional treatment for the patients after percutaneous coronary intervention: a systematic review and meta-analysis. Trop J Pharm Res 2022; 21(5): 1125-1134.*