

Familial Hypercholesterolemia with Two Mutations in LDLR Gene: A Case Report and Literature Review

Hui Zhou¹, Xiaoxiao Song¹, Bo Sun¹, Linjin Wu¹, Thachapol Napawan², Wei Gu^{1*}

¹Department of Endocrinology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

²Zhejiang University, Hangzhou, China

Email: *gu-wei@zju.edu.cn

How to cite this paper: Zhou, H., Song, X.X., Sun, B., Wu, L.J., Napawan, T. and Gu, W. (2017) Familial Hypercholesterolemia with Two Mutations in LDLR Gene: A Case Report and Literature Review. *International Journal of Clinical Medicine*, 8, 556-564.

<https://doi.org/10.4236/ijcm.2017.810052>

Received: September 11, 2017

Accepted: October 20, 2017

Published: October 23, 2017

Copyright © 2017 by authors and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

We report a case of Familial hypercholesterolemia (FH) with two mutations in low density lipoprotein receptor (LDLR) gene and speculate the correlation between the newly discovered mutation type of LDLR gene and FH. We collected and analyzed the clinical data of the proband in the case and her immediate family members, and detected the LDLR, Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK-9) and Apolipoprotein B (Apo B) gene in the peripheral blood of all the participants. We found that the curative effect of the patient is limited, but no obvious complication was detected. Genetic testing results pointed out that there were two mutations in the patient's LDLR gene. One was p.W483* mutation in exon 10 (c. 1448 G > A), another was p.T534I mutation in exon 11 (c. 1601 C > T). The p. W483* mutation in exon 10 was detected in the father and sister, additionally p. T534I mutation in exon 11 was detected in the mother. Both the two LDLR gene mutations are inherited from her parents. We hypothesize that the patient in this case was a complex heterozygote. The newly discovered mutation gene (T534I) may be one of the important causes of dyslipidemia in patients, and its adverse effects are more serious than W483* which have been reported. Also, we predict that the T534I mutation will not cause serious early onset of cardiovascular complications.

Keywords

Familial Hypercholesterolemia, Inherited Disease, Metabolism, Low-Density Lipoprotein Receptor, Gene Mutation

1. Introduction

Familial hypercholesterolemia (FH) is an inherited disease, which is reduced by

genetic defect and always characterized by abnormal metabolism of blood cholesterol [1]. Low density lipoprotein receptor (LDLR) gene mutation is the most common cause of FH. According to the severity, FH can be divided into two clinical manifestations: the relatively milder heterozygous form and more severe homozygous form [2]. It can usually be diagnosed definitely according to clinical features such as family history, blood lipid index, genetic testing and so on. At present, the therapeutic methods of FH mainly include changing lifestyle and drug treatment, in order to reduce blood lipids level and delay the progression of disease, eventually to prevent the occurrence of premature atherosclerotic cardiovascular disease. The research data among the world shows that the incidence of FH heterozygous patients is about 1/500, and about 50% of the male patients die of myocardial infarction and other cardiovascular complications before the age of 50 (female, before 60 years old) [3] [4] [5]. The morbidity of homozygous patients is 1/1,000,000 [5]. For the homozygous, the plasma low-density lipoprotein cholesterol (LDL-c) levels are higher, and body multiple xanthomas are more common. Some of the homozygous patients are more likely to an early onset and of cardiovascular diseases. Myocardial infarction (MI) even appears in some young people and even leads to death [5]. The life expectancy in the homozygous patients with standard lipid-lowering therapy is only 33 years old [6]. FH is the main risk factor of premature atherosclerosis, coronary artery stenosis and other cardiovascular disease, therefore early recognition and intervention can reduce the morbidity and mortality of cardiovascular events effectively [7] [8].

2. Case Report

The patient is a 21-year-old female, whose foot and hip skin were scattered in hard and painless nodules and masses nineteen years ago. The nodules recurred rapidly and increased to the size of soybeans several months later after mass resection in local hospital. And ten years ago, both bilateral knees, elbows, finger joints of the patient presented with similar bumps. The mass at the patient's left elbow was resected seven years ago, and histopathological diagnose was shown as "xanthoma". There was little symptomatic improvement, though she went to see a doctor many times at the department of dermatology and oncology.

The first time the patient visited the Department of endocrinology of our hospital is almost three years ago. There were multiple masses on knee, elbow, and multiple interphalangeal joint (sizes from rice to soybean, moderate hardness, poor mobility) (**Figure 1**) of the patient. And the level of serum total cholesterol (TC) was 14.1 mmol/L, low density lipoprotein (LDL) was 12.47 mmol/L. The patient was diagnosed with FH according to the medical history and the 2013 EAS Consensus of FH [9]. Since then, the patient has been given a therapeutic regimen with Atorvastatin and Ezetimibe Tablets successively. The serum lipid level and hepatic function are shown in **Table 1**. The sizes of the lumps on the skin are almost stable.



Figure 1. The nodules on the wrist (left) and between the fingers (right) of the patient (sizes from rice to soybean, moderate hardness, poor mobility).

Table 1. The lever of serum lipid and hepatic function after treatment.

Time period	Treatment regimens	TC (mmol/L)	LDL (mmol/L)	Remarks
2014.08	-	14.10	12.47	pretherapy
2014.8-2014.9	A 20 mg QD	12.44	10.07	normal liver function
2014.9-2015.5	A 40 mg QD	11.52	9.33	ALT70U/L, AST54U/L
2015.5-2015.7	A 20 mg QD; E 10 mg QD PPC 228 mg TID	9.6	8.08	ALT73U/L, AST64U/L
2015.7-2016.02	A 40 mg QD; E10 mg QD PPC 228 mg TID	13.74	11.3	ALT54U/L, AST43U/L
2016.02 till now	A 40 mg QD; E 10 mg QD PPC 456 mg TID	11.46	8.32	ALT49U/L, AST31U/L

RRs [10] [11]: TC < 5.18 mmol/L (200 mg/dL), LDL < 3.37 mmol/L (130 mg/dL). ALT < 34U/L, AST < 35U/L. *Abbreviations [A (Atorvastatin), E (Ezetimibe), PPC (Polyene Phosphatidylcholine Capsules), ALT (Alanine aminotransferase), AST (Aspartate transaminase), RRs (Reference ranges)].

2.1. Screening for Cardiovascular Complications

Electrocardiogram (ECG) was roughly normal. There were no obvious abnormality of the latest bilateral carotid and vertebral artery on ultrasound. The results of heart Doppler echocardiography indicated that the root of aortic is a thinner than normal, and the sinus tube junction is mild narrow (Figure 2). Coronary CTA was no obvious abnormality.

2.2. Genetic Testing

After detecting the peripheral blood of patients with LDLR, PCSK-9, Apo B gene, two mutation sites in LDLR gene were found: p.W483* in exon 10 (c. 1448G>A); p.T534I in exon 11 (c. 1601C > T), as shown in Figure 3(a) and Figure 3(b).

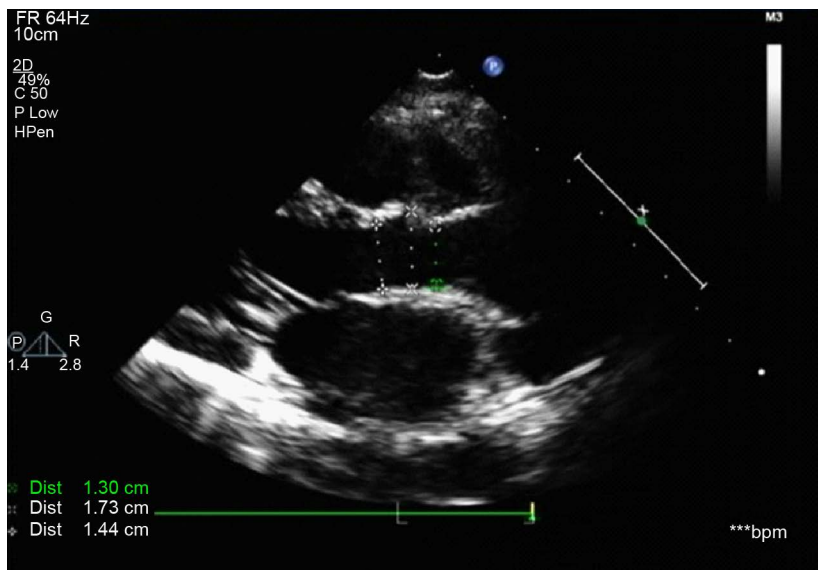


Figure 2. Aortic annular diameter is about 1.44 cm, and inner diameter of aortic sinus is about 1.73 cm. The sinus tube junction slant pipe wall is thickened, and inner diameter is about 1.30 cm.

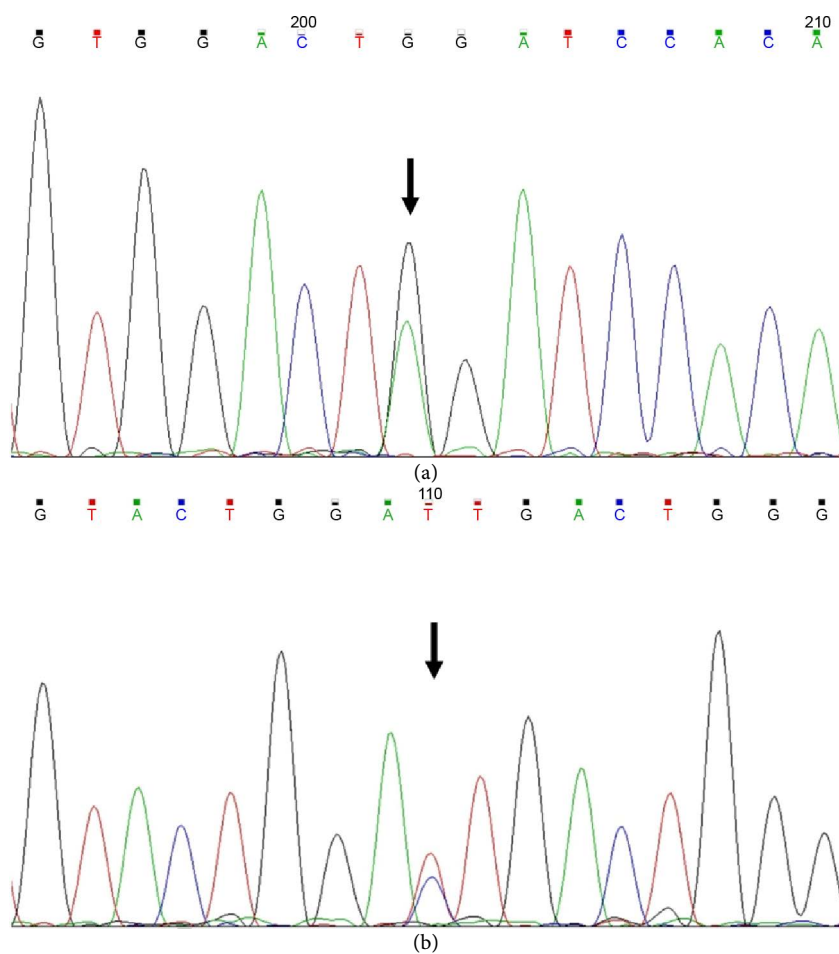


Figure 3. (a) p. W483* mutation (exon 10, c. 1448 G > A); (b) p.T534I mutation (exon 11, c. 1601 C > T).

2.3. Genealogical Analysis

We tested the LDLR gene and lipid level of the parents and elder sister. The same mutation site in exon 10 was detected in the father and sister, the same mutation was discovered in exon 11 of the mother. The blood lipid levels of them were all elevated, for details see attached **Table 2**. Nobody had received treatment with drugs. Related examinations had been conducted (such as: ECG, heart Doppler ultrasound, etc.).

3. Discussion and Literature Review

FH is a common inherited disease, which is consistent with Mendel's law of inheritance. And FH is autosomal and dominant, towards single gene inheritance. This disease is characterized by elevated levels of serum TC and LDL, and multiple nodular xanthomas are usually seen as the first symptoms of some patients. Gene mutations in the gene encoding are the major causes of FH, such as LDLR, Apo B, the PCSK-9, and LDLR gene mutations are the most common [2]. 50% of the FH patients have been confirmed with one or more mutations of LDLR gene [12], so gene detecting of LDLR is of great significance for the further research of the molecular basis of the pathogenesis of FH.

There are 1700 kinds of mutations in the LDLR gene reported on an international scale so far, domestic reports about 100 genotypes [5]. Gene mutations of Chinese patients with FH are in exon 1 - 17, and mutation of exon 18 has not been discovered, which is consistent with the worldwide mutation frequency [5]. In addition, among all 18 exons of LDLR, exon 4 (E4) mutations cases are the frequently found mutation, which may be related to the maximum chromosome span of E4 and the selection bias [5] [13].

The proband of this case owns two mutations, including paternal and maternal origination, and she is a complex heterozygous patient. Through the analysis of the gene sequence of the propositus, we drown the following results. The mutation in exon 10 (c. 1448 G > A/p. W483*) transformed the original tryptophan codon (UGG) into termination codon (UAG), and the protein expression was terminated prematurely. And another mutation p. T534I in exon 11 of LDLR gene (c. 1601 C > T/p. T534I) caused the transformation of amino acid codons from threonine (ACU) into isoleucine (AUU) as a missense mutation. At the same time, the average blood TC and LDL levels of the case are significantly higher than any other family members, so we speculate that the p.T534I mutation affects LDL metabolism.

Table 2. Gene detection results and blood lipid level of family members.

Relationship	Mutation site	TC (mmol/L)	LDL (mmol/L)
Father	p. W483* (exon 10)	7.90	5.16
Mother	p. T534I (exon 11)	10.62	6.70
Elder sister	p. W483* (exon 10)	7.56	4.50

The W483X mutation is one of the most common mutation types of LDLR gene in Chinese patients with FH. In this case, the patient's father and sister had the same mutation gene (p. W483*), and the serum lipid levels were similar and higher than normal. As early as 2009, Cheng and other scholars have reported the W483X gene mutation in exon 10, and this gene loci mutation causes a disturbed anabolic pathway of pro-EGF (epidermal growth factor precursor), which indirectly causes LDLR quantity and effective activity reduced, resulting in cholesterol metabolism disorders [14]. The content of LDLR in FH patients with this gene mutation was significantly lower than normal, and there is a remarkable correlation between p. W483* mutation and the onset of FH, atherosclerosis developed at a relatively early age, and progress rapidly, patients with severe p. W483* mutation phenotype should be treated as early as possible [15]. Maternal genetic testing showed p. T534I mutation in exon 11, and blood lipid level was higher than normal. It can be speculated that p. T534I mutation gene plays a role in LDL metabolism pathway. Compared with different lipid levels of patients who are carrying a single mutant gene, we speculate that the influence of new discovered p.T534I gene mutation on blood lipid metabolism is more serious than the mutation of p.W483*. But there is still no related report about p.T534I mutation gene in exon 11 at home and abroad. No obvious complications were detected of the proband and the mother who carries mutation p. T534I, so we speculate that the mutation will not lead to serious early onset of cardiovascular complications. And two mutations exist in LDLR gene of the proband, the long-term prognosis of which needs the essential follow-up attention.

For suspicious individuals with a clear history of xanthoma, especially with a family history, increased serum cholesterol, and (or) a family history of premature coronary heart disease (CHD), in addition to clinical laboratory examination, genetic detecting is needed as early as possible [16]. A series of research evidence indicated that among the patients with CHD before the age of 55 patients, 5% of them accompanied with FH [4]. The risk of FH patients with CHD increased 3.5 - 16 times compared to patients without FH, and serious gene mutations in homozygous patients are the decisive factors that increase the risk of cardiovascular disease (CVD) [17]. While the early recognition and treatment of individuals carrying defective genes can effectively reduce the risk of cardiovascular complications, but as a result of the complex and expensive detection technology of the LDLR molecule, the molecular detection cannot be well applied to the clinical setup.

Once the diagnoses of adult FH patients were established, lifestyle intervention should be started immediately. For patients with FH, low oil and fat is the most basic dietary requirements; in addition to appropriate physical exercise. Drug therapy mainly includes the maximum tolerated dose of statins, ezetimibe, bile acid sequestrants, etc. For the heterozygous patients merged CHD resistant to medication and the homozygous patients, continuous veno-venous hemofiltration (CVVH) should be taken [12]. For all children with FH, low-fat diet is

unfavorable before the age of two, and drug therapy can be given after the age of eight to ten [12]. Statins are still the preferred therapy regimens for FH now. But in most cases, single drug therapy usually cannot reduce LDL to the optimal level, especially for the homozygous [2]. Recently, a clinical study on the treatment with statins of FH patients by the European Medicines Agency (EMA) has approved that most adult patients or adolescents over 12 years old with homozygous FH need the combination of statins and other lipid-lowering methods to reduce serum cholesterol [18]. Controlling the serum blood lipids is the most effective strategy to reduce the risk of cardiovascular events in patients with FH. The research data show that only 15% of patients with FH can do regular medical visits [4], the vast majority of patients fail to achieve the lipid control objectives, or because of side effects, statins cannot be used at a standard treatment dose. Because of the damage of liver function, the therapeutic dose of statins of the patient in this case was not increased to a daily dose of 80 mg, and two lipid-lowering drugs were selected. The patient's lipid levels are still higher than normal but relatively stable, no obvious cardiovascular complications occurs.

A number of researches on gene therapy of FH have been carried out in recent years, there are numerous advanced developments, such as recombinant adeno-associated virus vector (AAV) carrying a LDLR transgene, induced pluripotent stem cell transplantation therapy, etc. [6]. With the contentious development of medical research, gene therapy is expected to be applied to the clinical treatment of FH in the near future.

4. Conclusion

The propositus of this case may be a homozygous patient according to existing clinical data and genetic testing results. A certain correlation exists between the p. T534I gene mutation in exon 11 and the pathogenesis of FH. And the p. T534I mutation may not cause serious early onset of cardiovascular complications. The effect of p.T534I mutation on the synthesis and function of LDLR is not clear, further experiments are needed to prove the correlation between the mutant gene and the pathogenesis of FH. Although there is no serious cardiovascular complication, the proband carries two mutations of LDLR gene which may lead to long-term hyperlipidemia. The patient in this case is likely to have an earlier onset of cardiovascular events than normal population. And long-term outcome requires further follow-up and attention. Because of the diversity of LDLR mutations, it is important to identify the type of mutations for the treatment of FH. At the same time, more researches on the pathway of LDLR metabolism are indispensable to achieve a definite diagnosis of the LDLR deficiency types in patients with FH.

Acknowledgements

This work was supported by grants from Zhejiang Provincial Medical and Health Technology Project (grand number 2013KYA089 and 2014KYA093), grants from

the Research Fund for International Young Scientists (grand number 81300083), and grants from Zhejiang Provincial Science and Technology Plan Project (grand number 2015C33170).

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article and regarding the funding that they have received. Informed consent was obtained from all individual participants included in the study.

References

- [1] Goldberg, A.C., Hopkins, P.N., Toth, P.P., Ballantyne, C.M., Rader, D.J., Robinson, J.G., *et al.* (2011) Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients: Clinical Guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology*, **5**, S1-S8. <https://doi.org/10.1016/j.jacl.2011.04.003>
- [2] Najam, O. and Ray, K.K. (2015) Familial Hypercholesterolemia: A Review of the Natural History, Diagnosis, and Management. *Cardiology and Therapy*, **4**, 25-38. <https://doi.org/10.1007/s40119-015-0037-z>
- [3] Vergopoulos, A., Knoblauch, H. and Schuster, H. (2002) DNA Testing for Familial Hypercholesterolemia: Improving Disease Recognition and Patient Care. *American Journal of Pharmacogenomics*, **2**, 253-262. <https://doi.org/10.2165/00129785-200202040-00005>
- [4] Qureshi, N., Humphries, S.E., Seed, M., Rowlands, P., Minhas, R. and Group, N.G.D. (2009) Identification and Management of Familial Hypercholesterolaemia: What Does It Mean to Primary Care? *British Journal of General Practice*, **59**, 773-776. <https://doi.org/10.3399/bjgp09X472674>
- [5] Dai, Y.F., Sun, L.Y., Zhang, X.B. and Wang, L.Y. (2011) Research Progression of LDLR Mutations in Chinese Familial Hypercholesterolemia. *Hereditas*, **33**, 1-8. <https://doi.org/10.3724/SP.J.1005.2011.00001>
- [6] Ajufo, E. and Cuchel, M. (2016) Recent Developments in Gene Therapy for Homozygous Familial Hypercholesterolemia. *Current Atherosclerosis Reports*, **18**, 22. <https://doi.org/10.1007/s11883-016-0579-0>
- [7] Turgeon, R.D., Barry, A.R. and Pearson, G.J. (2016) Familial Hypercholesterolemia: Review of Diagnosis, Screening, and Treatment. *Canadian Family Physician*, **62**, 32-37.
- [8] Palma, L., Welding, M. and O'Shea, J. (2016) Diagnosis and Treatment of Familial Hypercholesterolemia: The Impact of Recent Guidelines. *Nurse practitioner*, **41**, 36-43. <https://doi.org/10.1097/01.NPR.0000488711.52197.bd>
- [9] Nordestgaard, B.G., Chapman, M.J., Humphries, S.E., Ginsberg, H.N., Masana, L., Descamps, O.S., *et al.* (2013) Familial Hypercholesterolaemia Is Underdiagnosed and Undertreated in the General Population: Guidance for Clinicians to Prevent Coronary Heart Disease: Consensus Statement of the European Atherosclerosis Society. *European Heart Journal*, **34**, 3478-3490. <https://doi.org/10.1093/eurheartj/eh2273>
- [10] Kwo, P.Y., Cohen, S.M. and Lim, J.K. (2017) ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *American Journal of Gastroenterology*, **112**, 18-35. <https://doi.org/10.1038/ajg.2016.517>
- [11] Jellinger, P.S., Handelsman, Y., Bell, D.S., Bloomgarden, Z.T., Brinton, E.A., David-

- son, M., Fazio, S., Fonseca, V.A., Garber, A.J. and Grunberger, G. (2017) American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocrine Practice*, **23**, 479-497. <https://doi.org/10.4158/EP171764.GL>
- [12] Wang, B. and Lin, L. (2014) Recent Developments in the Clinical and Genetic Treatments of Familial Hypercholesterolemia. *Chinese Journal of Arteriosclerosis*, **8**, 148.
- [13] Austin, M.A., Hutter, C.M., Zimmern, R.L. and Humphries, S.E. (2004) Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: A Huge Prevalence Review. *American Journal of Epidemiology*, **160**, 407-420. <https://doi.org/10.1093/aje/kwh236>
- [14] Cheng, X., Ding, J., Zheng, F., Zhou, X. and Xiong, C. (2009) Two Mutations in LDLR Gene Were Found in Two Chinese Families with Familial Hypercholesterolemia. *Molecular Biology Reports*, **36**, 2053-2057. <https://doi.org/10.1007/s11033-008-9416-z>
- [15] Jiang, L., Sun, L.Y., Pan, X.D., Chen, P.P., Tang, L., Wang, W., et al. (2016) Characterization of the Unique Chinese W483x Mutation in the Low-Density Lipoprotein-Receptor Gene in Young Patients with Homozygous Familial Hypercholesterolemia. *Journal of Clinical Lipidology*, **10**, 538-546.
- [16] Vohnout, B., Gabcova, D., Huckova, M., Klimes, I., Gasperikova, D. and Raslova, K. (2016) Genetic Testing of Familial Hypercholesterolemia in a Real Clinical Setting. *Wiener Klinische Wochenschrift*, **128**, 916-921. <https://doi.org/10.1007/s00508-016-1053-2>
- [17] Hovingh, G.K. and Kastelein, J.J. (2016) Diagnosis and Management of Individuals with Heterozygous Familial Hypercholesterolemia: Too Late and Too Little. *Circulation*, **134**, 710-712. <https://doi.org/10.1161/CIRCULATIONAHA.116.023942>
- [18] Agabiti Rosei, E. and Salvetti, M. (2016) Management of Hypercholesterolemia, Appropriateness of Therapeutic Approaches and New Drugs in Patients with High Cardiovascular Risk. *High Blood Pressure & Cardiovascular Prevention*, **23**, 217-230. <https://doi.org/10.1007/s40292-016-0155-2>