

Familial hypercholesterolaemia: A South African perspective

Prof. NJ Crowther, PhD

Dr. JE Paiker MChB, FCPATH(SA)

Department of Chemical Pathology, National Health Laboratory Service, University of Witwatersrand Medical School

Correspondence: Nigel Crowther, Tel: 011-489 8559; Fax: 011-489 8451 or 717 2521

E-mail: nigelc@mail.saimr.wits.ac.za

Highlights - Hoogtepunte

- Prevalence and genetic features of familial hypercholesterolaemia in the Afrikaner, Ashkenazi Jewish, Gujerat Indian and African populations of South Africa.
- Clinical and biochemical features of familial hypercholesterolaemia.
- Approach to the treatment of familial hypercholesterolaemia.
- Prevalensie en genetiese eienskappe van familiële hipercholesterolemie (FH) in die Afrikaner, Asjkenasim Joodse, Goedjerat Indiër en Afrika-bevolkings in Suid-Afrika.
- Kliniese en biochemiese eienskappe van familiële hipercholesterolemie.
- Benadering tot die behandeling van familiële hipercholesterolemie.

SA Fam Pract 2003;45(3):43-47

SUMMARY

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder which results in patients having significantly increased levels of serum total cholesterol and low density lipoprotein (LDL) cholesterol. The high cholesterol levels are caused by a deficiency or a defect in the LDL receptor which results in severe and premature coronary artery disease.

Clinicians are able to diagnose this disorder by the clinical signs found on examination such as arcus and tendinous xanthomata, and the high cholesterol levels measured in the laboratory. Early and aggressive therapy using drugs and diet aims at decreasing the levels of cholesterol and thereby inhibiting the progression of coronary artery disease.

It is the intention of this article to present the pathophysiology, clinical and laboratory abnormalities of FH as well as the treatment options available to these patients.

INTRODUCTION

LDL-cholesterol is cleared from the circulation via the LDL-receptor which is found predominantly on hepatocytes, although the kidney, spleen, skeletal muscle and small intestine also play a role in LDL metabolism¹. Mutations in the gene encoding the LDL receptor, which is found on chromosome 19, lead to disruption of receptor function or lowered levels of the receptor at the cell surface, the consequence of which is a reduction of LDL clearance from the circulation and increased hepatic synthesis of cholesterol.

PREVALENCE OF FAMILIAL HYPERCHOLESTEROLAEMIA IN SOUTH AFRICA

Familial hypercholesterolaemia is a common genetic disorder with a prevalence of 1/500 in America and Europe.² Within South Africa, the prevalence is very high in particular population groups. Thus, in the Afrikaner population a prevalence rate of 1/72 has been reported,³ whilst in the

Ashkenazi Jewish population the prevalence is 1/67.⁴ It has also been stated that the Gujerat Indian community of South Africa has a high disease prevalence, although rates have not been published.¹

CLINICAL FEATURES OF FAMILIAL HYPERCHOLESTEROLAEMIA⁶

The severity of the clinical symptoms of FH depends on the number and the type of mutant LDL receptor genes that are inherited. Thus, the clinical and biochemical features of FH are less severe in heterozygotes than homozygotes because the heterozygotes have one copy of a normal LDL receptor gene, which will code for a functionally normal LDL receptor.

The major clinical features of FH are tendon and tuberous xanthomas which are the result of high serum cholesterol concentrations leading to tissue cholesterol deposition. The mechanism, by which this accumulation of cholesterol occurs, is not understood. The tendon xanthomas are usually found

on the extensor tendons of the knuckles and the Achilles tendons (see Figure 1) whilst the tuberous xanthomas occur on the elbows and knuckles. Xanthomas are present in childhood in homozygous FH patients but only appear, if at all, during adulthood in heterozygous FH patients. Interdigital xanthomas also occur and are diagnostic of homozygous FH. Xanthelasma, which are cholesterol deposits on the eyelids (see Figure 2) and corneal arcus (see Figure 3) are nearly always present in homozygous FH patients but are less frequent in heterozygotes.

Coronary artery disease (CAD) is very common in FH patients. The high serum LDL levels result in increased atherosclerotic plaque formation. Untreated, heterozygous, male FH patients will suffer from CAD before the age of 50 while females will present with symptoms 10 years later than this. Homozygous FH patients usually develop CAD before age 30, and in severe cases cardiovascular disease will occur during childhood. Aortic valve stenosis and articular symptoms such as tendonitis and arthralgias may also occur in FH homozygotes.

BIOCHEMICAL FEATURES OF FAMILIAL HYPER-CHOLESTEROLAEMIA

The main biochemical feature of FH is significantly raised serum total cholesterol and LDL-cholesterol levels. HDL-cholesterol concentrations are usually normal or reduced, whilst triglyceride concentrations are usually normal or slightly elevated (see Table 1).⁶ Homozygous FH patients have a more atherogenic lipid profile compared to heterozygotes, who in turn have higher cholesterol concentrations than non-FH subjects.

GENETIC FEATURES OF FAMILIAL HYPER-CHOLESTEROLAEMIA¹

The genetic defects that cause FH can be detected using standard gene mutation analysis methods involving polymerase chain reaction (PCR) and related technology. The mutations that occur in the LDL receptor gene can be

Figure 1: Xanthomas of the Achilles tendon

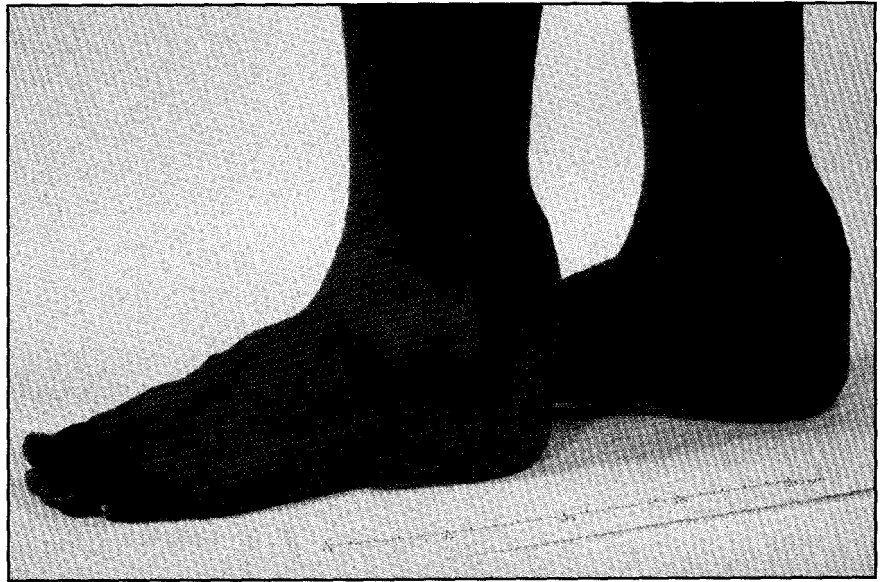


Figure 2: Xanthelasma (palpebral xanthomas)



Figure 3: Corneal arcus are visible as a white ring around the edge of the cornea

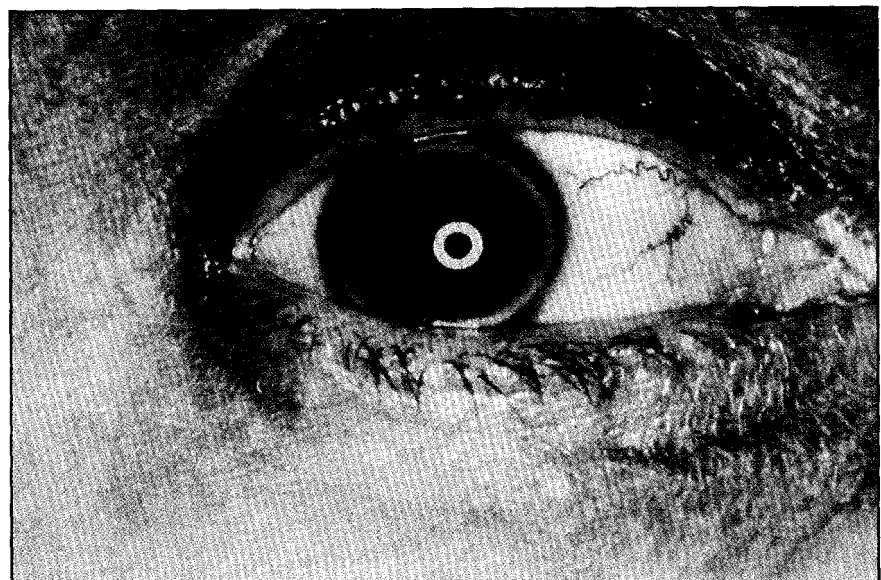


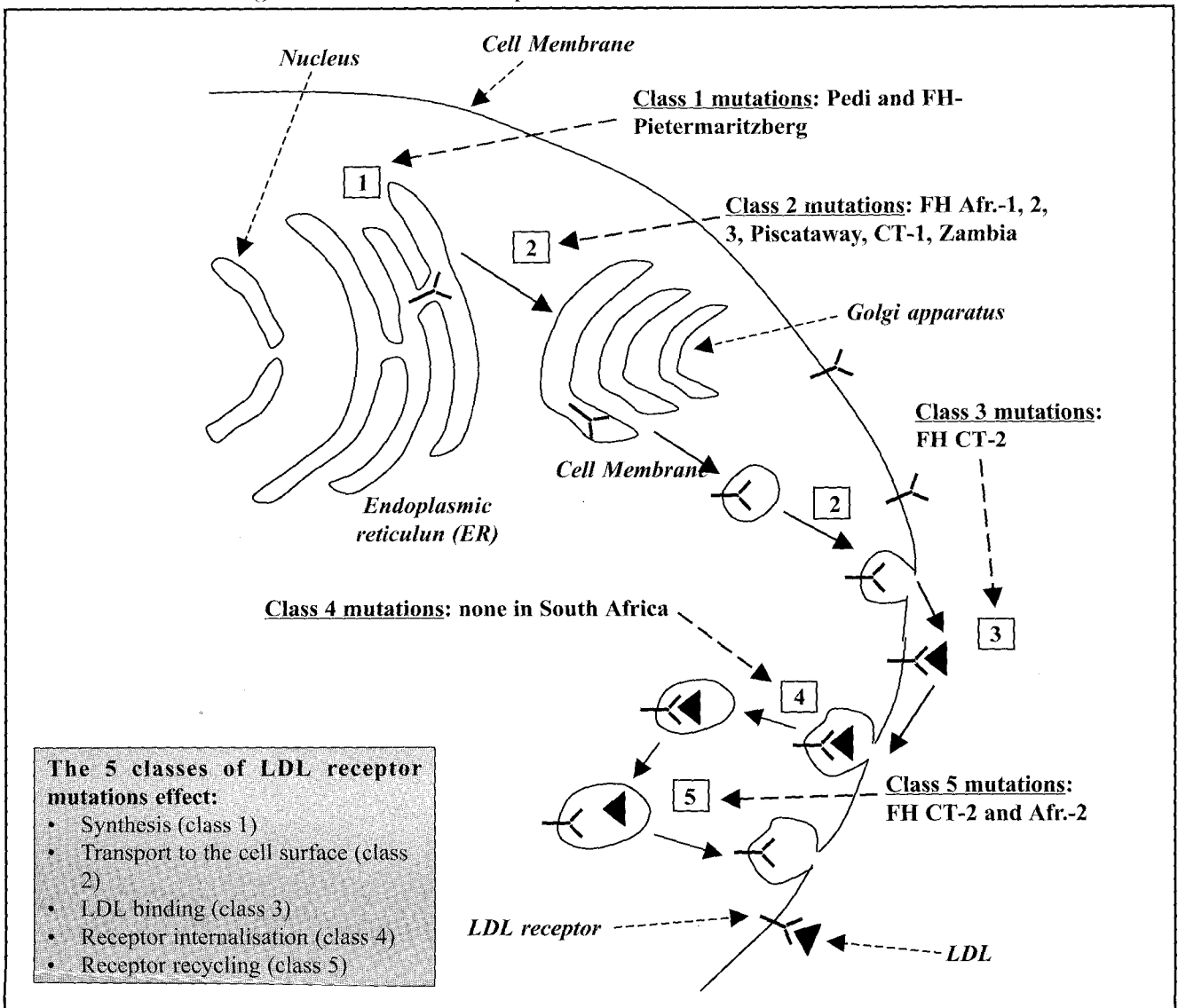
Table 1: Biochemical data for FH heterozygotic and homozygotic patients ^b			
	Non-FH subjects (n=20)	FH heterozygotes (n=20)	FH homozygotes (n=20)
Gender (M/F)	10/10	9/11	10/10
Age (years)	30.7 ± 4.2	32.9 ± 12.4	24.0 ± 9.2
Total cholesterol (mmol/l)	5.1 ± 0.6	8.2 ± 1.5**	14.9 ± 3.5**
LDL-cholesterol (mmol/l)	3.4 ± 0.6	6.6 ± 1.6**	13.5 ± 3.5**
HDL-cholesterol (mmol/l)	1.2 ± 0.5	1.1 ± 0.3	0.8 ± 0.2*
Triglycerides (mmol/l)	1.2 ± 0.6	1.0 ± 0.6	1.3 ± 0.6

Data are means ± SDs. *p<0.05 and **p<0.001 compared to the healthy, non-FH subjects.

classified into **five groups** according to how they affect receptor function (see **Figure 4**).¹ Some mutations can have more than one effect. Thus, FH Cape Town-2 reduces LDL binding and receptor recycling.

- **Class 1** mutations result in the complete absence of any receptor protein due to a block in synthesis of the receptor within the endoplasmic reticular compartment of the cell.
- **Class 2** mutations result in inhibition of the transport of the receptor to the cell surface. The LDL receptor is synthesized in the endoplasmic reticulum of the cell and from there is transferred to the Golgi apparatus. Vesicles bud off from the Golgi and transport the receptor to the cell membrane. The class 2 mutations

Figure 4: The LDL receptor mutations found in South Africa.



lead to either a complete (Class 2a) or partial (Class 2b) block in this complex subcellular transport pathway.

- The **class 3** mutations lead to receptors which do not bind their LDL ligand. The class 4 mutations produce functional LDL-binding receptors but these molecules are unable to be internalised within the cell after binding LDL.
- The final class of mutations is **class 5** and these produce a receptor that does not release its ligand after it has been internalised resulting in the receptor being trapped within the cell and not able to return to the cell surface.
- The **class 4 and 5** mutations disrupt the receptor recycling pathway which is very important in maintaining high levels of functionally active receptors on the cell surface.

Afrikaner community

The high prevalence of FH in the Afrikaner community of South Africa is probably due to a founder effect. The original colonists who gave rise to the present Afrikaner population came from Holland, France and Germany and numbered around 2000. Within this small community there was, by chance, a high prevalence of subjects carrying LDL receptor gene mutations. The prevalence of FH is far higher in the Afrikaner population than in the European populations from which these subjects were descended.

Ninety per cent (90%) of cases of familial hypercholesterolaemia in the Afrikaner community are due to 3 separate LDL receptor mutations termed FH Afrikaner-1, -2 and -3.⁷ The coloured population also carry these same 3 mutations plus a fourth mutation that has been called FH Cape Town-2^{8,9}.

Ashkenazi Jewish population of South Africa

The Ashkenazi Jewish population of South Africa also have a high prevalence of FH due to a gene founder effect, although this effect arose in the original community of Jewish people living in Lithuania. Indeed the gene mutation, termed FH Piscataway that explains most of the FH in this population is also

found in other Ashkenazi Jewish communities across the world¹⁰.

South African Indian population

Four different LDL receptor mutations have been found in the South African Indian population¹. It is thought that like the Ashkenazi Jews, the high prevalence of FH in this population is due to a founder effect that occurred in the founding population before they migrated to South Africa from the Gujerat region of India. The 4 mutations have been termed FH Zambia, FH Pietermaritzburg, FH Durban-1 and FH Durban-2.

African population

The African population by comparison, have a very low prevalence of FH. Two different mutations have been detected in African FH patients and these are known as FH Cape Town-1¹¹ and Pedi¹². However, a recent publication shows that mutations other than these may occur in the African population¹¹.

The study of the receptor mutations found in the various South African population groups has been instrumental in providing valuable information on both the structure-function relationships of the receptor and the control of the intracellular transport mechanisms involved in movement of the receptor to the cell membrane and the subsequent recycling of the receptor.

(See Figure 4).

TREATMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA⁵

The treatment of FH is primarily based on the reduction of LDL-cholesterol levels. Drug therapy is the major method used to reduce cholesterol levels however lifestyle management is also important particularly with regard to dietary intake of cholesterol and the avoidance of other risk factors that contribute to the development of CAD. The relative risk of developing CAD is 100 times greater in subjects with homozygous FH and this compares to a 2 fold higher risk in subjects who smoke when compared to non-smokers.

Treatment regimens depend upon the severity of the disease which in turn is dependent upon the LDL receptor

mutations. Patients who have an FH mutation in the homozygous state, which causes a complete block of receptor synthesis e.g. FH Pietermaritzburg will require the most intensive therapy and will have poor prognosis. Patients who carry a heterozygous mutation that gives rise to reduced numbers of functional LDL receptors on the cell surface e.g. FH Afrikaner-1 will have the best prognosis and will require less intensive treatment.

In homozygous patients, although dietary restriction is recommended the impact on LDL-cholesterol levels is minimal. In heterozygote FH patients dietary restriction can result in up to a 15% reduction in LDL levels in a compliant patient. The National Cholesterol Education Program (NCEP) recommends the following dietary intakes for patients with FH:¹³

Food category	Quantity
Cholesterol (mg/day)	<200
Total fat (% cal)	25-35
Saturated fat (% cal)	<7
Carbohydrate (% cal)	50-60
Protein (% cal)	±15%

Diets should be rich in whole grains, fruits and vegetables as fibre may have a cholesterol-lowering effect and these foods are rich in antioxidants, which may be cardioprotective.

A number of different drugs are available that reduce blood cholesterol levels. The most commonly used are the **statins**, e.g. atorvastatin (Lipitor®) and simvastatin (Zocor®). These agents reduce cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, one of the key enzymes involved in hepatic cholesterol synthesis. A newly introduced statin, rosuvastatin which is not yet available in South Africa, has been shown to reduce LDL levels by 40-69%. These agents have minimal side effects and strong cholesterol-lowering activity.

Nicotinic acid (Niacin®) also has hypocholesterolaemic properties and is often used as a cheaper alternative to the statins. The small risk of myositis from statin therapy is slightly increased if given in combination with niacin.

However, the side effects such as nausea and flushing make this drug a less popular therapeutic option.

Bile acid sequestrants (resins), e.g. cholestyramine (Questran®), colesvelam (Welchol®) reduce re-absorption of bile in the intestine and can safely be used in combination with the statins. However, the resin should be taken 1-2 hours after or 4-6 hours before other medications because the resin can reduce absorption of other drugs. The main drawback of this treatment is that resins cause constipation and therapy compliance can become a problem.

The **fibrates**, including gemfibrozil (Lopid®) and fenofibrate (Tricor®) have a lipid lowering action, the mechanism of which is not fully understood but may include reduction in hepatic lipoprotein synthesis. These agents reduce triglyceride levels and increase HDL concentrations but do not always effect LDL levels. Fibrates also produce gastric symptoms.

Probucol was introduced as a lipid lowering agent in the early 1980s. It has mild LDL-lowering effects but also reduces HDL levels, which reduces the utility of this drug. It has been found effective at reducing xanthoma size by promoting cholesterol efflux.

A new, powerful cholesterol-lowering agent, which is not yet available in South Africa has recently been introduced for treatment of hypercholesterolaemia. Ezetimibe specifically blocks intestinal cholesterol absorption and in clinical trials was able to reduce LDL levels by 15-20%. In combination with statin therapy an 18% reduction in serum LDL concentrations, above that induced by the statin alone, was observed.¹⁴

In homozygous FH patients with some residual LDL receptor function cholesterol-lowering agents may have some use in conjunction with bile acid sequestrants or niacin and reduction of dietary cholesterol intake. In FH patients with no receptor function, more aggressive treatment is required. These include apheresis to filter out the LDL particles from the blood. This is carried out every one or two weeks but is expensive and not available to most South African FH patients. Liver transplantation can also be performed to provide a source of functional hepatic LDL receptors, but this is very rare due

to the adverse complications of major organ transplantation and continual immunosuppression.

Portacaval anastomosis have been used for treating FH homozygotes and have produced up to a 50% reduction in LDL levels and regression of xanthomas. The mechanism by which this occurs is not known.

The prognosis for many homozygous FH patients in South Africa is poor. Improvements in therapy, including advances in gene replacement may hold some hope for the future. Gene therapy has been used to treat FH patients¹⁵ leading to significant reductions in LDL levels, which were unfortunately not sustained. Advances in gene replacement technology are necessary and attainable and gene therapy may eventually be the one treatment capable of restoring complete LDL receptor function in patients with homozygous FH mutations.

CONCLUSIONS

Familial hypercholesterolaemia is a devastating disease, particularly in the homozygous form. However, a large body of medical and biochemical data is now available and this knowledge has allowed the development of genetic screening techniques and new forms of therapy that have led to more effective management of FH patients and a concomitant reduction in CAD and mortality rates. Genetic diagnosis of FH has been a major breakthrough and has allowed the development of population screening programmes, pre-clinical diagnosis and early introduction of drug therapy¹⁶. Furthermore, genetic counselling of families is now available and is recommended for all FH patients to inform them of the disease risk in their offspring.

Despite these advances in our knowledge premature mortality in FH patients is high. However, new developments in both drug and genetic therapy hold hope for the future and will lead to further improvements in the quality of life and the prevalence of CAD in FH patients. □

Please refer to CPD Questionnaire on page 56.

Acknowledgements

The authors would like to thank Professor Derick Raal for his advice on the manuscript content and for supplying photographs.

References

- Rubinsztein DC, van der Westhuyzen DR, Coetzee GA. Monogenic primary hypercholesterolaemia in South Africa. *SAfr Med J* 1994; 84: 339-344.
- Goldstein JL, Brown MS. Familial hypercholesterolaemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The metabolic basis of inherited diseases*. 6th ed. New York: McGraw-Hill, 1989; 1216-1250.
- Steyn K, Goldberg YP, Kotze MJ, et al. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. *Hum Genet* 1996; 98: 479-484.
- Schfel HC, Baker SG, Jenkins T, Mendelsohn D. Prevalence of familial hypercholesterolaemia in Johannesburg Jews. *Am J Med Genet* 1989; 34: 545-547.
- Citkowitz E. Hypercholesterolaemia, familial. <http://www.emedicine.com/med/topic1072.htm>
- Paiker JE, Raal FJ, Waisberg R, Buthelezi EP. Quantity versus quality of LDL cholesterol in patients with familial hypercholesterolaemia – which is more important? *Clin Chim Acta* 2001; 314: 167-173.
- Kotze MJ, Langerhoven E, Warnich L, Du Plessis L, Retief AE. The molecular basis of familial hypercholesterolaemia in South African Afrikaners. *Ann Hum Genet* 1991; 55: 115-121.
- Van der Westhuyzen DR, Stein ML, Henderson HE, Marais AD, Fourie AM, Coetzee GA. Deletion of two growth factor repeats from the low-density lipoprotein receptor accelerates its degradation. *Biochem J* 1991; 278: 667-682.
- Loubser O, Marais AD, Kotze MJ, et al. Founder mutations in the LDL receptor gene contribute significantly to the familial hypercholesterolaemia phenotype in the indigenous South African population of mixed ancestry. *Clin Genet* 1999; 55: 340-345.
- Metner V, Landsberger D, Berkman N, et al. A common Lithuanian mutation causing familial hypercholesterolaemia in Ashkenazi Jews. *Am J Hum Genet* 1991; 49: 443-447.
- Thiart R, Scholtz CL, Vergotine J, et al. Predominance of a 6bp deletion in exon 2 of the LDL receptor gene in Africans with familial hypercholesterolaemia. *J Med Genet* 2000; 37: 514-519.
- Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolaemia. *Human Mutation* 1992; 1: 445-466.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). *JAMA* 2001; 285: 2486-2497.
- Farnier M. Ezetimibe in hypercholesterolaemia. *Int J Clin Pract* 2002; 56: 611-614.
- Grossman M, Rader DJ, Muller DW, et al. A pilot study of *ex vivo* gene therapy for homozygous familial hypercholesterolaemia. *Nat Med* 1995; 1: 1148-1154.