ORIGINAL ARTICLE

Genetic Causes of Familial Hypercholesterolaemia in a Malaysian Population

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Summary

A total of 86 unrelated Malaysian patients with familial hypercholesterolaemia (FH) were studied for mutations in their low-density lipoprotein receptor (LDL-R) gene. Amongst them, 23 had a LDL-R gene mutation, while none having an Apolipoprotein B-3500 (Apo B-3500) mutation.

Patients with the LDL-R gene defect appeared to have a higher level of low-density lipoprotein cholesterol (LDL-C), an increased incidence of xanthomas and coronary heart disease (CHD), but no relationships were found between the type of LDL-R gene mutations and their lipid levels or clinical signs of CHD.

In contrast to Western data, our findings seemed to indicate a predominance of mutations in the ligand binding domain and an absence of Apo B-3500 gene mutation. The latter finding may offer a genetic basis as to why Asian patients with familial hypercholesterolaemia have lower LDL-C levels and less premature CHD than their Western counterparts.

Key Words: LDL-R, LDL-C, HDL-C, Apo B-3500, Hyperlipidaemia, Coronary heart disease, Xanthomas, Familial Hypercholesterolaemia, Denaturing gradient gel

Introduction

Familial hypercholesterolaemia (FH) which is caused by defects in the low density lipoprotein receptor (LDL-R) gene is an autosomal dominant disorder with a frequency in the Western World of about 0.2%[1]. Characteristically FH heterozygotes have a two to three fold increase in plasma low density lipoprotein cholesterol (LDL-C) associated with tendon xanthomata, arcus senilis and they often develop symptomatic coronary heart disease (CHD) in the fourth to the sixth decade of life.

The primary cause of FH is a mutation in the gene of the LDL-R, which are responsible for the catabolism of the plasma LDL-C and of its precursor lipoproteins. A considerable number of LDL-R gene defects have been reported[2], showing thereby the heterogenicity of the disease.

These mutations have been found in many populations of different ethnic background, although some mutations have been found predominantly in certain ethnic groups like the French Canadians and Afrikaners. Most gene defects have originally been detected by restriction fragment length polymorphism (RFLP), but this method only detects a limited number of point mutations, small deletions or insertions.

Therefore other methodology, including denaturing gradient gel electrophoresis (DGGE) followed by sequencing as used here, is more appropriate.

It has been shown recently that heterozygote FH patients in Asia are much less affected by premature CHD and tendon xanthomata than their Western counterparts[3]. The role of LDL-R gene mutations in this observation is unknown since limited data is available on the occurrence of LDL-R gene defects in the Asian Pacific region.

Our study aims to confirm the different phenotypic expression of FH in a Malaysian population, compared to Europe and to examine if the nature of the LDL-R gene mutation can provide an explanation for this phenomenon.

Materials and Methods

Eighty six patients, who attended the lipid clinic of one of the authors (KKL) during the last two years, were selected on the basis of the diagnosis of primary hypercholesterolaemia with a total cholesterol (TC) level higher than 7.0 mmol/L, a triglyceride (TG) level of lower than 4.0 mmol/L, the absence of a secondary cause of hyperlipidaemia (such as diabetes, hypothyroidism and nephrotic syndrome), and a dominant pattern of inheritance of hypercholesterolaemia. The ethnic origins (Malay, Chinese, and Indian), sex and age were recorded for all patients.

In each patient a search for clinical evidence of FH (arcus seniles, xanthelasmata, xanthoma) and of CHD (positive stress test, symptom of angina pectoris, history of acute myocardial infarction, PTCA or CABG) was conducted.

Blood was taken by the first author in his clinic for analysis and for DNA investigation after an overnight fast. The blood sampling took place in 1995 and 1996. The patients were fully informed about the investigations and all agreed upon. At that time an oral informed consent was accepted internationally as being compliant with Good Clinical Practice (GCP). The DNA investigation was carried out at the University Hospital in Ghent, Belgium.

The procedure at the University Hospital stipulates that an Ethics Review Board (ERB) approval is mandatory for all DNA investigations. In the application to the ERB board it was mentioned that an oral and not a written informed consent was obtained from the patients. The ERB board agreed with it and permission was given to do the study. Because of this no submission was done to a local ERB. Indeed in international studies it is common that one ERB approval covers all centres worldwide participating in the study. Therefore it must not be considered unusual that a study done in Malaysian patients is covered by a Belgian ERB.

Lipid determination

The measurements of total plasma cholesterol, HDL-cholesterol, and triglyceride were carried out using commercially available kits (Boehringer Mannheim). LDL-C concentrations were calculated using the Friedewald formula[4].

Assessment of LDL receptor mutations

Genomic DNA was prepared from whole blood[5]. All 18 exons were amplified separately; with 1 of the 2 primer pair containing GC-clamp necessary for denaturing gradient gel electrophoresis analysis[6].

The primer sequences used were as follows:

Exon 1A:5' TTC TGG CGC CTG GAG CAA GCC TT-3' Exon 1B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCA TTG AAA TGC TGT AAA TGA CGT-3' Exon 2A: 5'AAA ATA AAT GCA TAT CAT GCC CA-3' Exon 2B: 5'-GCG CCG

CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCC TTT CTC CTT TTC CTC TCT CTC-3' Exon 3A: 5'-AAA TAG CAA AGC AGG GCC ACA CT-3' Exon 3B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GTG ACA GTT CAA TCC TGT CTC TTC-3' Exon 4A: 5'-TGG TCT CGG CCA TCC ATC CCT GC-3' Exon 4B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC ACG CAG AAA CAA GGC GTG TGC CA-3' Exon 5A: 5'-CAA CAC ACT CTG TCC TGT TTT CC-3' Exon 5B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GGG AAA ACC AGA TGG CCA GCG CTC-3' Exon 6A: 5'-GCA AGC CGC CTG CAC CGA GAC TC-3' Exon 6B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GTC CTT CCT CTC TCT GGC TCT CAC-3' Exon 7A: 5'-AGG GCT CAG TCC ACC GGG GAA TC-3' Exon 7B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CGC CCG CCG CCG CCG CCC GAG TCT GCA TCC CTG GCC CTG CGC-3' Exon 8A: 5'-CCA CCC GCC GCC TTC CCG TGC TC-3' Exon 8B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCC AAG CCT CTT TCT CTC TCT TCC-3' Exon 9A: 5'-CCT GAC CTC GCT CCC CGG ACC CC-3' Exon 9B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GGG CTG CAG GCA GGG GCG ACG CTC-3' Exon 10A: 5'-ATG CCC TTC TCT CCT CCT GCC TC-3' Exon 10B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GAG CCC TCA GCG TCG TGG ATA CGC-3' Exon 11A: 5'-TGG CTG GGA CGG CTG TCC TGC GA-3' Exon 11B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCA GCT ATT CTC TGT CCT CCC ACC-3' Exon 12A: 5'-CTT CGA TCT CGT ACG TAA GCC AC-3' Exon 12B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GTC TCC TAA TCC ACT TGT GTG TCT-3' Exon 13A: 5'-GTT TCC ACA AGG AGG TTT CAA GG-3' Exon 13B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GGT CAT CTT CCT TGC TGC CTG TTT-3' Exon 14A: 5'-GAC GCC CCG CCC CCA CCC TGC CCC-3' Exon 14B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCC TGA CTC CGC TTC TTC TGC CCC-3' Exon 15A: 5'-AGA AGA CGT TTA TTT ATT CTT TC-3' Exon 15B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GGT GTG GTG GCG GGC CCA GTC TTT-3' Exon 16A: 5'-CGC TGG GGG ACC GGC CCG CGC TT-3' Exon 16B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GCC TCA CTC TTG CTT CTC TCC TGC-3' Exon 17A: 5'-TGG CTT TCT AGA GAG GGT CAC AC-3' Exon 17B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CCG CCG CCG CCG CCC GTG ACA GAG CGT GCC TCT CCC TAC-3' Exon 18A: 5'-GCT TTG GTC TTC TCT GTC TTT GA-3' Exon 18B: 5'-GCG CCG CGC CCG TCC CGC CGC CGC CGC CCG CCG CCG CCG CCC GTC CGC TGT TTA CCA TTT GTT GGC-3'

Denaturing gradient gel electrophoresis (DGGE)

Gel gradients were optimized for every polymerase chain reaction (PCR) product and gradient gels were prepared by mixing a 80% and a 100% denaturant solution (40% deionised formamide and 7M urea make a 100% denaturant solution). The gels were stained in ethidium bromide after a 20 hour run in 1 X TAE buffer at 60°C and 20mA per gel and examined under UV illumination [6,7].

Assessment of the Apo B-3500 mutation

The Apo B-3500 mutation was detected by PCR amplification of the fragment of exon 26 of the Apo B gene, containing the Apo B-3500 mutation and restriction digestion with MspI followed by electrophoresis on agarose gel[7].

Cloning and sequencing of the mutations

The PCR product was cloned in a TA vector (TA cloning kit - Invitrogen). White colonies were picked up and a second PCR was done to separate the cloned "wild type" fragment from the cloned homoduplex fragment. A large-scale plasmid preparation was prepared on the positive colonies and sequencing was done with the Thermo Sequenase dye cycle sequencing kit (Amersham Life Science) or Dynabeads M-280 (Dynal, Oslo, Norway) after PCR amplification.

Table I
Characteristics of the population with and without LDL-receptor gene defect

Parameter	Total population of unrelated patients screened	Total population of unrelated patients with a LDL receptor gene mutation	Total population of unrelated patients without a LDL receptor gene defect	Difference between patients with and without gene defects	
	n = 86	n = 23	n = 63	P>|T|	P>|Chi-sqs|
Age (years)	54±11	53±11	55±11	NS	-
Sex (M/F)	41/45	12/11	29/34	-	NS
Ethnic origin					
Malay	13/86 (15.1%)	2/23 (8.7%)	11/63 (17.5%)	-	NS
Chinese	72/86 (83.7%)	20/23 (87.0%)	52/63 (82.5%)	-	NS
Indian	1/86 (1.2%)	1/23 (4.3%)	0/63 (0%)	-	NS
Lipid levels (mmol/L)					
TC	8.8 ±1.3	9.3±1.2	8.7 ±1.3	+	P≤0.10 by +
TG	2.0± 0.9	2.0 ±0.9	2.0 ± 0.8	NS	-
HDL-C	1.3 ± 0.17	1.3±1.2	1.3 ±0.3	NS	-
LDL-C	6.6 ±1.3	7.2 ±1.2	6.5 ±1.3	*	-
Xanthoma (%)	41/86 (47.7%)	15/23 (65.2%)	26/63 (41.3%)	-	*
Arcus (%)	27/85 (31.8%)	9/23 (39.1%)	18/62 (29.0%)	-	NS
Evidence of CHD (%)	33/86 (38.4%)	13/23 (56.5%)	20/63 (31.7%)	-	**
PTCA/CABG	25/84 (29.8%)	11/23 (47.8%)	14/61 (23.0%)	-	*
AMI/AP	24/85 (28.2%)	9/23 (39.1%)	15/62 (24.2%)	-	NS
Positive Stress ECG	28/76 (36.8%)	14/23 (60.9%)	14/53 (26.4%)	-	**
Type I or II diabetes (%)	6/85 (7.1%)	2/23 (8.7%)	4/62 (6.5%)	-	NS
Hypertension (%)	29/85 (34.1%)	6/23 (26.1%)	23/62 (37.1%)	-	NS

*+, *, ** : P ≤0.1, 0.05 and 0.01 respectively*
NS : Not significant at P≤0.05

Table II
Characteristics of 23 unrelated patients with a LDL receptor gene defect

Patient Number	Regionl affected	Initial patient (ethnic origin)	Sex	Age	Lipid levels (mmol/l)				Clinical signs				
					TC	TG	HDL-C	LDL-C	Arcus senilis	Xanthoma	PTCA or CABG	AMI or AP	Stress ECG
243	PROMOTER	CTS (Ch)	M	62	8.1	1.0	1.7	5.0	1	1	1	1	1
387	Exon 2	MYC(Ch)	M	31	9.2	2.4	1.0	7.1	0	1	0	0	0
260	Exon 3	TKC (Ch)	M	63	8.7	2.3	1.0	6.7	0	0	1	0	1
392	Intron 3	TCT.(Ch)	F	64	12.0	3.9	0.8	9.4	1	1	0	0	1
188	Exon 4	HKP(Ch)	M	53	8.0	0.2	0.8	7.1	1	1	1	0	1
316		KKM(Ch)	M	61	10.4	3.5	2.9	5.9	1	0	1	0	0
349	Exon 5	WWF(Ch)	M	44	11.0	1.7	0.9	9.3	1	1	0	0	0
262		SSY(Ch)	F	44	8.9	0.9	1.4	7.1	0	0	0	0	0
246	Exon 6	SV(Ind)	F	53	8.6	2.5	1.3	6.2	0	0	0	0	0
155	Exon 7	TCH(Ch)	F	59	10.0	3.4	Ø	Ø	1	1	1	1	1
159		LCS(Ch)	F	44	9.5	1.2	1.1	7.9	0	1	1	1	1
150	Exon 8	KAH(Ch)	F	63	7.9	1.6	Ø	Ø	0	1	1	1	1
212		LZ(Mal)	F	51	8.1	1.1	2.3	5.3	0	1	1	1	1
176	Exon 9	LKM(Ch)	F	66	10.0	3.1	1.2	7.4	0	0	1	0	0
183		MY(Mal)	M	52	8.3	1.9	0.9	6.5	0	1	1	0	1
441		OSB(Ch)	M	48	8.8	2.4	1.0	6.7	1	1	0	1	1
452		LSB(Ch)	F	40	8.4	1.9	Ø	Ø	1	1	0	0	Ø
175	Exon 10	YTP(Ch)	F	31	8.5	1.4	0.9	6.9	0	1	0	0	0
213		GLYK(Ch)	F	54	8.6	1.0	0.9	7.2	0	0	0	0	0
255	Exon 12	TBT(Ch)	M	68	11.7	2.7	1.4	9	0	0	1	1	1
178	Exon 14	HCY(Ch)	F	53	9.9	0.9	1.4	8.1	0	0	0	0	0
180		CCP(Ch)	M	71	7.1	1.8	1.3	5.0	0	0	1	1	1
393		CM(Ch)	M	44	9.6	2.6	1.7	6.7	0	1	0	0	0

Ch: Chinese, Mal: Malay, Ind: Indian, M: Male, F: Female
Lipid levels (in mmol/l) are based on record before treatment
Clinical signs: Ø: Not done or not known 0 : Negative 1 : Positive

Statistical analysis

Descriptive statistics were expressed as means ± standard deviation (SD). Two sided unpaired t-tests were applied to the results for comparison of lipid values between groups. Test of difference in proportions or incidence between groups were performed. The remaining results were analyzed by Chi-Squared.

Results

A total of 86 unrelated patients (48% men, mean age=54 years with range 31 to 71 years) were studied. Of these 23 showed a point mutation in the LDL receptor gene. No patients were found with an Apo B-3500 type of mutation.

Their ethnic origins were Chinese (84%), Malay (15%) and Indian (1%).

Thirty six percent of the subjects possessed high TG levels as well (>2.2 mmol/L), and in 47.6% of the subjects, xanthoma was detected by clinical examination. CHD was clinically evident in 34.5% of the subjects, while hypertension was diagnosed in 34.1% of the cases. Diabetes (Type I or Type II) was less common (7.1%).

The characteristics of the unrelated patients with and without a LDL-R gene defect are shown in Table I.

Of the 23 patients showing a point mutation of the LDL receptor gene, 20 were of Chinese origin (87%), 2 of Malay origin (8.7 %) and 1 of Indian origin (4.3%). The mean age in this group was 53 years (range: 31 - 71 years) and the ratio of men/women was 12/11.

It may be seen from Table I that the group with the LDL-R gene defect and the group without the defect were similar in age, sex and ethnic origin distribution as well as were TC, TG and HDL-C levels. Their incidence of arcus, hypertension and diabetes was also similar. The patients with a LDL-R gene mutation however had significantly higher LDL-C levels ($P<0.05$) and a significantly higher incidence of xanthoma ($P<0.05$) and of CHD ($P<0.01$), when compared to the patients without a LDL-R mutation. Among the CHD symptoms, patients with a LDL-R gene mutation had significantly higher incidence of having PTCA/CABG ($P<0.05$) and positive stress ECG ($P<0.01$) than those without a LDL-R mutation.

Table II summarises characteristics of the 23 unrelated patients with a LDL-R mutation. In the 20 unrelated Chinese patients with LDL receptor gene defects, point mutations in the promoter region (1 patient), exon 2 (1 patient), 3 (2 patients), 4 (2 patients), 5 (2 patients), 7 (2 patients), 8 (1 patient), 9 (3 patients), 10 (2 patients), 12 (1 patient) and 14 (3 patients) were found. In the 2 unrelated patients of Malay ethnic origin with LDL receptor gene defects, point mutations in exons 8 and 9 were found. The only Indian patient with a LDL receptor gene defect had a point mutation in exon 6.

Of the 23 unrelated patients with a LDL receptor gene defect, 1 (4%) had a mutation in the promoter region, while 8 (35%) had a mutation in the ligand binding domain (exon 2 to 6), of which 2 (9%) were in exon 4.

Point mutations in the epidermal growth factor (EGF) precursor homology domain (exons 7 to 14) were seen in 14 patients (61%). Other individual characteristics on lipid profiles and clinical expressions of the patients with a LDL receptor gene defect are also given in Table II. These data showed that there was no association between the type of LDL-R gene mutation on the one hand and lipid levels or clinical signs of atherosclerotic disease on the other hand.

Discussion

To the best of our knowledge, this is the first extensive study of LDL-R gene and apo B gene defects in a Malaysian population. The subjects were obtained from one of the largest lipid private clinics in Malaysia and are therefore supposed to be quite representative, at least, for the Chinese ethnic group in that country.

As reviewed by Hobb et al[2] the LDL-R gene located on the distal short arm of chromosome 19 span 45 kilobases (kb) is composed of 18 exons and 17 introns. Exon 1 encodes the signal sequence. Exons 2 - 6 encode the ligand binding domain. Exons 7 - 14 encode a region for epidermal growth factor (EGF) precursor homology.

Exon 15 encodes 0-linked sugars domain. Exons 16 and 17 are for membrane-spanning while part of exons 17 and 18 are the cytoplasmic domain. In addition, the 5' - flanking region of the LDL-R gene serves as promoter for gene transcription. This rather long and complex gene offers much opportunity for mutations in various sites (introns and exons). Indeed, more than 150 naturally occurring LDL-R mutations mainly from American, Canadian, European, African background have been characterized at a molecular level[2].

In the present study, defects were found in almost all exons of LDL-R gene, ranging from the promoter, exon 2 to exon 14 (except exons 1, 11, 13). 35% of the LDL-R mutation occurred in ligand binding domain while 61% of the LDL-R mutation fell in the epidermal growth factors (EGF) precursor homology domain. Mutations in the tail part of the gene, i.e. O-linked sugars domain (exon 15), membrane-spanning domain (exons 16 and 17) and the cytoplasmic domain (exons 17 -18) however were not demonstrated. Additionally, no Apo B-3500 defect was found.

In China, a total of 29 LDL-R gene mutations has been reported[3,8]. Sun et al[3] reported 11 LDL-R gene mutation which included exon 4, exons 11-14 and exon 17 in 10 homozygous FH and their parents from Jiang-Su province. Mak et al[8] described 18 LDL-R gene mutations scattering through the promoter and 10 exons of the LDL-R gene in the 21 patients studied in Hongkong. Mutation in the Apo B-3500 gene was not detected in these two studies.

In Japan, a broad spectrum of mutations in the LDL-R gene of the Japanese population has been demonstrated as well. Studies on Japanese FH have shown wide range of LDL-R gene mutations, scattering over the promoter and exons 1 to 18 of the gene[9-17].

In comparison with data obtained from European and US lipid clinics, two striking observations can be made about the Malaysian sample: the predominance of mutations in the epidermal growth factors (EGF) precursor homology domain over mutations in the ligand binding domain, and the absence of Apo B-3500 defects. Indeed in a similar study done in Belgium and France[18], it was reported that 55% of observed LDL-R gene mutations occurred in the ligand-binding domain, compared to only 35% in the Malaysian sample. The difference appeared even more striking when exon 4 was considered. Only 9% of the observed Malaysian mutations occurred in exon 4 compared to 31% in the French-Belgium population.

On the other hand, 61% of the Malaysian mutations occurred in the EGF precursor domain, compared to 42% in the French-Belgian population.

Recently, Depuydt et al[18] published data concerning a mutation in exon 4, which appeared to be particularly linked to severe CHD[19]. Others have emphasized the important role of mutations in the ligand binding domain in general and in exon 4 in particular[20] in the pathogenesis of CHD, because this exon is known to be critical for interaction with the ligands of Apo E and Apo B.

Mutations in the ligand binding domain have been found to be associated with higher LDL-C levels and probably also with a higher risk of CHD. Our data of less frequent mutations in exon 4 in an Asian population could therefore be put forward as a partial explanation for the less severe and less frequent incidence of CHD in this population. It also could provide a genetic basis for the lower lipid levels in this population. However, more data are necessary to confirm this hypothesis.

The absence of Apo B-3500 mutations in our study was unexpected when compared with the US and European data. The frequency in Europe of this type of mutation can indeed be as high as 8% in a familial hyperlipidaemic population[21]. It can be concluded from the European data that the Apo B-3500 mutation is a significant genetic cause of hypercholesterolaemia and of CHD in some European countries[21,22]. This however does not seem to be the case in our Malaysian population. The absence of this mutation in the latter group could therefore be another genetic reason why familial hyperlipidaemic patients of Asian origin have lower lipid levels and less premature CHD than Western subjects.

The characteristics of Malaysian patients with and without LDL-R gene defect showed a significant

difference in LDL-C levels, as well as in some clinical signs of CHD (xanthoma & CHD incidence). Data in the literature are discordant towards the effects of the Apo B and LDL-R gene mutations on lipid levels and incidence of CHD. Hegele et al[23] and Coresh et al[24] found a higher risk for CHD in Apo B gene mutated patients while Pan et al[25] did not confirm this.

Lombardi et al[26] and Sun et al[3], the latter in a Chinese population, found no higher LDL-C or TC levels in patients with a LDL-R gene mutation, compared to patients without a LDL-R mutation. Steyn et al[27] however reported opposite findings. Bertolini et al[28] also found no association between certain type of LDL-R gene mutations and incidence of CHD.

Hence, there seems to be a contradiction between our findings and those of Sun et al[3] in a Chinese population, but diet and other environmental factors may explain the difference.

We know that some FH patients die of a heart attack in their forties, while others remain symptom free through to old age. One possible reason for this is because of the specific LDL-R mutations they have inherited and in support of this is the observation that the age of onset of CHD tends to aggregate in families with hyperlipidaemia. Moreover there are some published data to indicate that some mutations might respond better to certain drugs than others[29,30]. Knowledge of the type of mutations in LDL-R could therefore be of help to practising physicians in prescribing the most appropriate drug of treatment for the individual FH patient.

Another beneficial impact of the DNA diagnosis of FH is the creation of an awareness and the understanding of the disorder in the family and in particular the possibility of an earlier treatment of the children. Indeed atherosclerosis starts in childhood and those at risk will benefit from early identification and treatment, by reducing their risk of CHD.

In conclusion, we hypothesize that the lower lipid levels and the less frequent incidence of premature CHD in the Malaysian population and in other Asian populations in general could possibly be determined genetically by way of the different nature of the LDL-R gene mutation, with a milder phenotypic expression, possibly in combination with the absence of the Apo B-3500 type. Further studies are however necessary to confirm this hypothesis. Since the detection of mutations in FH patients is of importance to the practicing clinician, in relation to choice of treatment and optimum response, the application of biotechnology technique in the identification of the nature of LDL-R gene mutation of other genetic defects should be introduced to benefit the public and to help stamp the rising trend of CHD mortality in this country.

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