



## Hypercholesterolemia, Familial

### Alternative Names

FHC  
FH  
Hyperlipoproteinemia, Type II  
Hyperlipoproteinemia, Type IIA  
Hyper-Low-Density-Lipoproteinemia  
Hypercholesterolemic Xanthomatosis, Familial  
LDL Receptor Disorder

### Record Category

Disease phenotype

### WHO-ICD

Endocrine, nutritional and metabolic diseases >  
Metabolic disorders

### Incidence per 100,000 Live Births

101- ~

### OMIM Number

143890

### Mode of Inheritance

Autosomal dominant

### Gene Map Locus

19p13.2, 1q21-q23, 9q22-q31, 8p21-p12, 7p15,  
3p21.2-p14.1

### Description

Familial hypercholesterolemia is an autosomal dominantly inherited deficiency of low density lipoprotein receptors, which are normally synthesized in the liver. The disorder is characterized by markedly elevated serum cholesterol bound to low density lipoprotein, resulting in hypercholesterolemia, xanthomas, and premature atherosclerosis of the coronary arteries.

It is estimated that several millions of persons could suffer from the disorder worldwide, frequencies varying between 1/150 and 1/500 births depending on populations. One in every two persons may be affected in a family where one individual has been identified as having familial hypercholesterolemia.

### Molecular Genetics

Autosomal dominant hypercholesterolemia can be caused by mutation in the low density lipoprotein receptor gene, LDLR, which is a cell surface receptor that plays an important role in cholesterol homeostasis. The LDL receptor is an 839-amino acid protein rich in cysteine, with multiple copies of the Alu family of repetitive DNAs, and is synthesized as a 120-kD glycoprotein precursor that undergoes change to a 160-kD mature glycoprotein through the covalent addition of a 40-kD protein.

### Epidemiology in the Arab World

#### Bahrain

Lehrman et al. (1985) genetically investigated a Bahraini patient with FH. They found that this patient has a change in the tryptophan-792 codon (TGG) to a stop codon (TGA) in the LDLR gene.

Al-Mahroos and McKeigue (1998) studied the prevalence of diabetes and associated risk factors in the population of Bahrain. In 2,128 Bahrainis aged 40-69 years. Age-standardized prevalence of diabetes was 25% in Jaafari Arabs, 48% in Sunni Arabs, and 23% in Iranians. Mean plasma cholesterol was 0.5 mmol/l higher in diabetic than in normoglycemic participants, 0.5 mmol/l higher in Sunni than in Jaafari Arabs, and, excluding diabetic individuals, 0.2 mmol/l higher in those with a positive family history of diabetes than in those with a negative family history. Al-Mahroos and McKeigue (1998) concluded that the high rates of diabetes in Bahrain and other Arabian Peninsula populations appear to be part of a familial syndrome that includes raised plasma cholesterol levels. Risk is related to ethnic origin but not to parental consanguinity.

Shawar et al. (2012a) described a novel LDLR mutation in two unrelated Arab families with Familial Hypercholesterolemia. The first of these families consisted of eight living and four deceased individuals. All the deceased expired of premature CHD. Of the living, two were normal, whereas the remaining six were diagnosed with hypercholesterolemia. The second family consisted



of 11 individuals, nine of whom were diagnosed with hypercholesterolemia. All patients investigated molecularly showed a c.1706-2-A>T substitution at the junction of intron 11 and exon 12. Splicing prediction algorithms predicted a new cryptic splice site downstream of this original position, generating a 10-bp deletion from the beginning of exon 12, predicted to result in nonsense mediated decay. Extended relatives of one of the families, living in another Arab Gulf country, were found to have the same mutation. Shawar et al. (2012a) called this "the Arabic allele". In a separate study, Shawar et al. (2012b) studied the prevalence of hypercholesterolemia among 166 apparently healthy non-smoker university students (aged between 16-30 years) in Bahrain. The population consisted of 85 Saudis and 81 Bahrainis. A total of 44 students (19 males, 25 females) were found to have hypercholesterolemia. Eight of these students reported a family history of cardiac events, while five of them were obese with a BMI >30.

#### **Kuwait**

Olusi et al. (1997) carried out a study on a hospital outpatient population of 1076 subjects with a mean age of 38.9 years and a male to female ratio close to one, to determine the prevalence of hypercholesterolemia in Kuwait. The prevalence of hypercholesterolemia was found to constitute 15.8% of the cohort, 16% in males, and 15.7% in females. Moreover, the prevalence of hypercholesterolemia in middle-aged (40-49 years) Kuwaiti males was found to comprise 22.2% of the cohort proposing an increased risk of coronary heart disease in one of every five Kuwaiti middle-aged males. Furthermore, Olusi et al. (1997) found extremely high prevalence rate (43.2%) of hypercholesterolemia in females aged 50-59 years and 31.2% in females aged 60-69 years.

Selvan et al. (2007) described the clinical features and family history of an 11-year old Kuwaiti boy with homozygous familial hypercholesterolemia. The patient presented with a history of recurrent episodes of chest pain and multiple xanthomas. Upon examination, he was found to have clinical features of moderate aortic stenosis and aortic regurgitation. ECG showed ST depression in the anterior and inferior leads, and thickened aortic valve with moderate regurgitation. Angiogram showed 70% stenosis of the left main coronary artery and ostial stenosis of the right coronary artery. Lipid profile was grossly abnormal. Pedigree analysis of his family revealed an interesting history. Both this father and paternal grandmother, who died at the age of 50-years following a myocardial infarction, were hypercholesterolemic. Of his siblings, two of either sex, had died after suffering from recurrent chest

pain and multiple xanthomas, while three others had multiple xanthomas and hypercholesterolemia and were under treatment. Two other siblings were normal. The patient was managed with beta-receptor agonists, vasodilators, anti-thrombotics, cholesterol lowering drugs, and analgesics. However, he succumbed on the fourth day to severe coronary heart disease, emphasizing the need for early diagnosis of familial cases of hypercholesterolemia.

#### **Lebanon**

Edwards et al. (1978) studied fasting serum cholesterol and triglyceride levels in 131 randomly selected adult members of a Lebanese Community of Western New York. Mean cholesterol levels (males, 217 mg%; females 234 mg%) were higher than those reported from the Lebanon but similar to those reported in most other populations. Mean triglyceride levels (males, 153 mg%; females, 115 mg%) were higher than those reported in most other populations. Twenty-three subjects were hyperlipidemic on the basis of age and frequency distribution adjusted serum lipid levels above the 90th percentile. Clinical and family studies carried out on 13 of these 23 hyperlipidemic subjects suggested that 77% had monogenic hyperlipidemia and 23% primary non-monogenic hyperlipidemia. A high frequency of familial hypercholesterolemia (minimum estimate 0.7%) was found, in keeping with the high frequency of the disorder in Lebanon.

Lehrman et al. (1987) studied 4 unrelated Arab patients with homozygous familial hypercholesterolemia, 3 from Lebanon and 1 from Syria. These patients were found to have a nonsense mutation (CYS660TER) in the LDLR gene. Lehrman et al. (1987) referred to this mutation as the Lebanese allele.

#### **Oman**

Al-Hinai et al. (2012) described an Omani family with hypercholesterolemia due to mutations in the LDLR gene. The proband was a 9-year old female, born to consanguineous parents, who presented with arcus cornealis, xanthelasmata of the eyes, xanthomas of the elbows, and thickenings of both the Achilles tendons. Her lipid profile was hypercholesterolemic, stress test was strongly positive for myocardial ischemia, and ECG showed mild thickening of the mitral valve. Both of her parents and two sisters were also hypercholesterolemic. Her father had CAG that showed significant 3-vessel disease. DNA analysis of the proband, her father and two sisters revealed a mutation in the LDLR gene in all. The proband was treated with statins in combination with LDL apheresis. The family refused an atriovenous fistula.



### **Palestine**

In 5 Christian-Arab kindreds, Oppenheim et al. (1991) found the 'Lebanese' allele in correlation with familial hypercholesterolemia. In addition, their results suggested the possible existence of an independent factor contributing to elevated LDL-cholesterol levels.

### **Saudi Arabia**

[See: Bahrain > Shawar et al., 2012b].

### **Syria**

Vergopoulos et al. (1997) presented findings suggesting the existence of a xanthomatosis susceptibility gene in a consanguineous Syrian kindred containing 6 individuals with homozygous FH. Half of the homozygotes had giant xanthomas, while half did not, even though their LDL-cholesterol concentrations were elevated to similar degrees (more than 14 mmol/l). Heterozygous FH individuals in this family were also clearly distinguishable with respect to xanthoma size. By DNA analysis they identified a hitherto undescribed mutation in the LDLR gene in this family: a T-to-C transition at nucleotide 1999 in codon 646 of exon 14, resulting in an arginine for cysteine substitution. Segregation analysis suggested that a separate susceptibility gene may explain the formation of giant xanthomas.

[See also: Lebanon > Lehrman et al., 1987].

### **United Arab Emirates**

Agarwal et al. (1995) conducted a study to determine if elevated cholesterol is a problem in the United Arab Emirates in order to be able to evaluate the contribution of cholesterol as a risk factor for atherosclerosis in this environment. Volunteers were recruited at busy urban public sites. Data on age, sex, nationality, weight, blood pressure and smoking history were collected, and blood samples were taken for estimation of total cholesterol, hemoglobin and individual blood group. A raw data set was developed, with calculation of body mass index and subsequent statistical analysis carried out on a PC using the SPSS programme. In the 834 patients, there were 19 nationalities represented which were pooled into 7 groups (5 Arab and 2 non Arab) according to their ethnic origins. The prevalence of hypercholesterolemia varied from 47.2-53% in the Arab Nationals. The mean cholesterol levels of the Arab subgroups were similar and showed no difference, statistically. Similarly, within the Arab subgroups, the median cholesterol levels were no different. No statistical difference was found in the distribution of cholesterol (high, borderline high or desirable levels) among the seven ethnic groups.

Hypercholesterolemia appears to be a problem in most nationalities living within the UAE. Overall, it afflicts nearly 50% of the adult population. Although the ethnic Arab groupings have a wide range of socioeconomic attributes, the similarity of the distribution of cholesterol may point to an underlying innate genetic etiology or an environmental cause such as dietary overindulgence, or both.

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