American Journal of Epidemiology
Copyright © 2004 by the Johns Hopkins Bloomberg School of Public Health
All rights reserved

Vol. 160, No. 5
Printed in U.S.A.
DOI: 10.1093/aje/kwh237

Familial Hypercholesterolemia and Coronary Heart Disease: A HuGE Association Review

Melissa A. Austin[1], Carolyn M. Hutter[1], Ron L. Zimmern[2], and Steve E. Humphries[3]

[1] Institute for Public Health Genetics and Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA.
[2] Public Health Genetics Unit, Strangeways Research Laboratory, University of Cambridge, Cambridge, United Kingdom.
[3] Center for Genetics of Cardiovascular Disorders, British Heart Foundation Laboratories, Department of Medicine, Royal Free and University College London Medical School, London, United Kingdom.

Received for publication November 24, 2003; accepted for publication April 26, 2004.

Familial hypercholesterolemia (FH) is an autosomal disorder characterized by increased levels of total cholesterol and low density lipoprotein cholesterol. The FH clinical phenotype has been shown to be associated with increased coronary heart disease and premature death. Mutations in the low density lipoprotein receptor gene (*LDLR*) can result in the FH phenotype, and there is evidence that receptor-negative mutations result in a more severe phenotype than do receptor-defective mutations. Mutations in the apolipoprotein B-100 gene (*APOB*) can result in a phenotype that is clinically indistinguishable from familial hypercholesterolemia, and mutations in this gene have also been shown to be associated with coronary heart disease. Preliminary research indicates that the FH phenotype is influenced by other genetic and environmental factors; however, it is not clear if these are synergistic interactions or simply additive effects.

APOB; coronary disease; epidemiology; genetics; hypercholesterolemia, familial; *LDLR*; receptors, LDL

Abbreviations: CI, confidence interval; FH, familial hypercholesterolemia; LDL, low density lipoprotein; SMR, standardized mortality ratio.

Editor's note: *This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm).*

GENES AND GENE VARIANTS

The genetic causes of heterozygous familial hypercholesterolemia (FH) have been a subject of study since the early 1900s (1), and they have already been reviewed for the Human Genome Epidemiology Network (2). Briefly, the frequency of FH is reported as 1/500 for Caucasian populations (3). FH is characterized by autosomal inheritance of increased total cholesterol and low density lipoprotein (LDL) cholesterol, primarily attributable to mutations in the low density lipoprotein receptor gene (*LDLR*) (4, 5). *LDLR* is located on chromosome 19 at 19p13.1-p13.3 (6), and over 700 mutations have been identified in this gene (7, 8). Mutations in two other genes also cause the clinical FH phenotype. One of these is the apolipoprotein B-100 gene (*APOB*), located on chromosome 2p23-24 (9, 10), that codes for the protein component of LDL particles (11). In contrast to *LDLR*, only a small number of functional mutations have been identified in *APOB*. The third gene, proprotein convertase subtilisin/kexin type 9 (*PCSK9*), was recently identified on chromosome 1p32 (12). To date, no epidemiologic research has investigated mutations in *PCSK9*.

LDLR mutations can be classified according to the effect they have on LDL receptor protein function (13). The LDL receptor protein is a cell surface receptor that removes LDL particles from the plasma by way of receptor-mediated endocytosis. In class 1 mutations, the LDL receptor protein is not synthesized; in class 2 mutations, the LDL receptor is not transported to the Golgi; in class 3 mutations, the LDL receptor does not properly bind with the LDL particles; in class 4 mutations, bound surface receptors are not internal-

Correspondence to Dr. Melissa A. Austin, F 363 Health Sciences Building, Box 357236, School of Public Health and Community Medicine, University of Washington, 1959 NE Pacific Avenue, Seattle, WA 98195 (e-mail: maustin@u.washington.edu).

ized; and in class 5 mutations, the internalized LDL particles are not released in the endosome. The majority of mutations identified to date are class 2 or class 3 mutations occurring in the ligand-binding and epithelial growth factor precursor regions of the gene (14). Class 1 mutations are alternatively referred to as "null" or "receptor-negative" mutations in the literature, whereas mutations from classes 2–5 are termed "receptor defective." For this review, we will use the terms "receptor negative" and "receptor defective."

DISEASE

Coronary heart disease and its clinical manifestation of myocardial infarction are widely recognized to be a multifactorial disorder, with contributions from both environmental and genetic factors. The development of hypertension and diabetes, both of which also have environmental and genetic components, is strongly associated with increased coronary heart disease risk (15). Increasing age and male gender are strongly associated with coronary heart disease risk, with men typically developing clinically important disease 10–15 years before women, who in general are protected to a degree until after menopause (16). Of the environmental factors, smoking is the major contributor and is associated with a roughly twofold higher lifetime risk (17). Lack of exercise and the associated adiposity, as well as a high intake of saturated fats and a low intake of certain vitamins, are also associated with increased risk (16). The mechanism of action of these factors is thought at least in part to be through determining differences in the plasma levels of lipids and lipoproteins that are atherogenic. High levels of LDL cholesterol and low levels of high density lipoprotein cholesterol have consistently been shown to be associated with coronary heart disease risk (18). Evidence of the strong genetic component for coronary heart disease risk is supported by the consistent association between a reported family history of early coronary heart disease and a personal increased risk (19), with risk associated with family history being in the order of 1.7-fold higher, even after adjusting for other classical risk factors (20). Although such analyses do not distinguish between familial aggregation of environmental or lifestyle risk factors and inherited factors, these data strongly support the role of inherited factors in the mechanisms of coronary heart disease.

The specific genes involved in these processes and their variants in the general population are the subject of much research but are beyond the scope of this review. With an estimated heterozygous frequency of 1/500 (3), FH accounts for only a small fraction of the familial cases of FH. Another gene that has been well examined in the context of coronary heart disease is the gene coding for the apolipoprotein E (*APOE*). This association has previously been reviewed for the Human Genome Epidemiology Network (21). There are three common variants of this gene called *E3*, *E2*, and *E4*, with the *E4* allele being associated with higher and the *E2* allele being associated with lower levels of plasma apolipoprotein B-containing proteins such as LDL (22). As would be expected from the known risk associated with LDL cholesterol levels, carriers of the *E4* allele tend to have higher and carriers of the *E2* allele tend to have lower coronary heart disease risk (23), such that these common variants explain from 2 percent to 3 percent of the population variance in coronary heart disease risk.

The first stage of the development of the atherosclerotic lesion is thought to be dysfunction of the vessel wall endothelium, which in healthy vessels maintains vascular tone and blood pressure. Endothelial dysfunction can be detected in the peripheral vessels of subjects with high coronary heart disease risk factors (such as FH) as early as in the first decade of life (24). Animal models suggest that endothelial dysfunction is caused by a wide range of insults, including inflammatory processes (25) as a result of infectious agents, smoking, or elevated levels of lipoproteins such as LDL. When LDL enters the vessel wall through a dysfunctional endothelial barrier, the LDL particles are oxidized and recruit monocytes from the blood. These cells take up the LDL and may then exit the site of the lesion, allowing the damage to be limited and healed. However, in subjects with high plasma levels of LDL, this process is overwhelmed, and the monocytes, differentiated into macrophages, become lipid laden and "foamy" in appearance under the microscope (26). These macrophage-foam cells are the hallmark of the developing atherosclerotic lesion. In later stages, the burden of toxic lipids results in cellular death and the deposition of cholesterol as crystals in the expanding atherosclerotic plaque (27).

Although the plaque itself may occupy an increasing proportion of the lumen and thus restrict blood flow, this is not associated with clinical symptoms until stenosis approaches 70 percent or greater (27). At this stage, ischemia may develop, especially upon exercise, and is seen as the chest pains of angina. The clinically more serious event of a myocardial infarction occurs if the plaque ruptures. The resulting thrombus may completely occlude the already narrowed vessel and, downstream, ischemia may cause permanent damage to the myocardial tissue. If the affected area of the heart is extensive or localized in a critical region, the result may be fatal.

Rupture occurs due to the degradation of the vessel wall matrix by metalloproteinases (28). Much research interest is currently focused on the cellular and tissue control of expression of these enzymes and their natural inhibitors, as well as on the role of common genetic variants and environmental mediators, such as inflammation and smoking. However, one of the major determinants of both the initiation of vessel damage and the rate of development of the atherosclerotic lesion seems to be plasma levels of key lipoprotein particles, including LDL levels. Further research on FH and on the impact of treatment in FH patients will continue to enhance our understanding of the relations between LDL levels and coronary heart disease.

ASSOCIATIONS

We identified studies of FH and coronary heart disease through two methods. First, to identify classic papers in the early literature, we performed hand searches of papers in our collections and the reference lists of extensive review articles (3, 29). Second, we searched MEDLINE and PubMed using combinations of the terms "familial hypercholester-

olemia," "*LDLR*," "*APOB*," "apolipoprotein B," "coronary heart disease," and "cardiovascular disease," in addition to "genetics" and "epidemiology." Studies that examined noncoronary vascular disease outcomes, such as stroke (30), peripheral vascular disease (31), and intima-medial wall thickness (32), are reviewed separately for the Human Genome Epidemiology Network (33).

Studies detailing the magnitude of the association between clinical FH and coronary heart disease are listed by geographic location in table 1 and Web table 1. (This information is described in the first of three supplementary tables; each is referred to as "Web table" in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm) as well as on the *Journal*'s website (http://aje.oupjournals.org/).) Table 1 is limited to studies that provide a risk estimate for the association, whereas Web table 1 lists all studies with a control group and includes additional information on the prevalence and cumulative probability of coronary heart disease in FH and control populations. The following discussion of the association studies is organized by study design to highlight the primary findings and to identify methodological limitations.

Studies estimating cumulative probability of coronary heart disease

In one of the earliest association studies, Slack (34) compared 104 patients who had type II hyperbetalipoproteinemia (clinical FH) with 41 patients who had type III, type IV, or type V hyperlipoproteinemia (hypertriglyceridemia) in the United Kingdom. Medical records and resting electrocardiogram results were obtained, and index patients were followed for 1–10 years. The cumulative probability of a first attack of ischemic heart disease by age 60 was higher for patients with clinical FH (85.4 percent for males, 57.5 percent for females) than for patients with type III, type IV, or type V hyperlipoproteinemia (53.3 percent for males, 25 percent for females). Soon afterward in the United States, Stone et al. (35) examined 1,023 first- and second-degree relatives of 116 FH index patients diagnosed at the National Institutes of Health from 1964 to 1970. The risk of fatal or nonfatal coronary heart disease by age 60 years was 52 percent for male and 31.8 percent for female relatives with FH compared with 12.7 percent and 9.1 percent for relatives without FH. Additional studies determined a similarly high risk of premature coronary heart disease among patients with clinical FH in Japan (cumulative probability of myocardial infarction by age 60 years: ~35 percent for males, ~20 percent for females) (36), in Quebec (mean age of onset of ischemic heart disease: ~40 years for males, ~50 years for females) (37), in France (mean age of onset of ischemic heart disease: 44.2 years for males, 53.1 years for females) (38), and in Norway (cumulative probability of coronary heart disease symptoms by age 60 years: 83 percent for males, 70 percent for females) (39). Because the latter four studies did not include a control group, the magnitude of association could not be estimated, and they are not included in table 1 or Web table 1.

Although recent studies have also found an association between clinical heterozygous FH and coronary heart disease (40, 41), the early studies described above were performed before the widespread use of statins for treatment of hypercholesterolemia and, thus, give a more accurate reflection of the natural history of the disease. However, the early studies have two primary limitations. First, the life-table analyses for some studies included deceased relatives (35, 36). Second, index patients were selected from hospitals (34, 35, 38) or lipid clinics (36, 37), and some had a prior history of coronary heart disease or xanthomatosis. As a result, these study subjects may have had a more severe form of FH or may have other genetic/environmental predisposing factors for coronary heart disease compared with a population-based sample. Both of these biases could spuriously inflate the observed association.

Taken together, however, the results of these studies uniformly demonstrate an increased burden of premature coronary heart disease and death associated with the presence of FH. In general, the onset of disease appears to be delayed approximately 10 years for women compared with men (37, 38) and is lower in Japan (36) than in Western countries.

Cohort studies of standardized mortality ratios for coronary heart disease and all-cause mortality

Jensen et al. (42) prospectively followed 331 individuals (181 with FH, 150 normocholesterolemic) in 11 Danish families from 1944 to 1964. Again, a high prevalence of early coronary heart disease was seen in FH patients (45.1 percent for males by age 50 years). An increased number of deaths for FH-affected relatives was observed compared with the general Danish population. An indirect standardization was performed. The national death rate for each 10-year age bracket, by sex, for 1943–1964 was reported by the Copenhagen statistics department, and these rates were used to calculate the expected number of deaths for the study population's size in each age and sex bracket. The resulting standardized mortality ratio of observed to expected deaths was elevated for both sexes (males: standardized mortality ratio (SMR) = 2.88, 95 percent confidence interval (CI): 1.73, 4.46; females: SMR = 1.71, 95 percent CI: 0.912, 2.93). This increase was not observed for the unaffected relatives (SMR = 1.03, 95 percent CI: 0.562, 2.01). A Japanese study (43) examined 527 heterozygotes over 10 years and observed 41 deaths. Thirty patients died from coronary heart disease, a number 10.9 times higher than the proportional mortality of cardiovascular deaths in the general Japanese population. In addition, the mean age of death from a cardiac event was significantly younger for males (54 years) than females (68 years).

The Simon Broome Familial Hypercholesterolemia Register Group has been recruiting patients from lipid clinics in the United Kingdom since 1980. The first publication of findings from this large prospective cohort study presented data on 526 patients for a total of 2,234 person-years from 1980 to 1989 (44). The second publication expanded the size of the cohort to a total 1,185 patients followed for 8,770 person-years from 1980 to 1995 (45). The observed number of deaths was compared with the number expected on the bases of age, sex, and calendar period death rates for the

TABLE 1. Association studies of clinical familial hypercholesterolemia and coronary heart disease by geographic location

Country/ethnicity	Study sample and study design	Study definition of coronary heart disease	Risk measure used	Risk measure value	Reference
Asia					
Japan/Japanese	Cohort of 527 FH† heterozygotes examined between 1976 and 1986 from Konazawa Hospital in Japan; FH defined as 1) TC† of >230 mg/dl with tendinous xanthomata or 2) TC of >230 mg/dl and first-degree relative fulfilling criterion 1	Clinical history, electrocardiogram irregularity, and/or transient increase of serum enzymes	PMR† for coronary heart disease compared with that of the Japanese population	PMR = 10.9 (95% CI†: 7.95, 15.03)**	Mabuchi et al., 1986 (43)
Europe					
Denmark/Danish	Family study of 11 Danish families followed from 1944 to 1964: *n* = 181 members (84 males and 97 females) classified as hypercholesterolemic (TC of >350 mg/dl for people aged ≥15 years and >300 for people aged <15 years); *n* = 150 (75 males and 75 females) classified as normocholesterolemic	Clinical history or diagnoses by study author	SMR† for all-cause mortality indirectly standardized by age, sex, and calendar period rates in the Danish population	Males aged 10–79 years: SMR = 2.88 (95% CI: 1.73, 4.46)**; females aged 10–79 years: SMR = 1.71 (95% CI: 0.912, 2.93)	Jensen et al., 1967 (42)
The Netherlands/Dutch	Family study of 855 first-degree relatives (426 males and 429 females) of 113 index patients analyzed over 32,048 person-years; index patients were outpatients at a lipid clinic between 1988 and 1990; criteria for heterozygous FH: mean fasting serum TC of ≥8 mmol/liter and tendinous xanthomata and/or hypercholesterolemia in first-degree relatives	Angina pectoris, 70% stenosis, myocardial infarction, coronary bypass, or percutaneous transluminal coronary angioplasty	SMR for all-cause mortality for all relatives (assume only 50% affected) compared with age, sex, and calendar period rates in the Dutch population	All first-degree relatives aged 1–103 years: SMR = 1.34 (95% CI: 1.16, 1.55)*	Sijbrands et al., 2000 (47)
The Netherlands/Dutch	Pedigree analysis traced back to a single pair of ancestors in 1830; limited to complete sibships with individuals living ≥20 years from 1830 to 1989; 250 descendants identified in lines with living descendants carrying the *LDLR V408M* mutation	Not reported	SMR for all-cause mortality for all relatives on transmission lines (assume only 50% affected) compared with age, sex, and calendar period rates in the Dutch population	All pedigree members from 1830 to 1989: SMR = 1.32 (95% CI: 1.03, 1.67)*	Sijbrands et al., 2001 (46)
United Kingdom/British	Cohort study of 526 patients with FH (282 males and 244 females); patients were recruited from 1980 to 1989 and followed prospectively for 2,234 person-years; FH defined by TC of >7.5 mmol/liter and tendinous xanthomata in patient or second-degree relative	Myocardial infarction or angina	SMR for coronary heart disease indirectly standardized by age, sex, and calendar period rates in Britain and Wales	Both sexes aged 0–79 years: SMR = 3.86 (95% CI: 2.10, 6.39)*	The Simon Broome Register Group, 1991 (44)
United Kingdom/British	Cohort study of 1,185 patients with FH (605 males with a median age of 40.3 years and 580 females with a median age of 43.9 years); patients recruited from 1980 to 1995 and followed prospectively for 8,770 person-years; FH defined by TC of >7.5 mmol/liter and tendinous xanthomata in patient or second-degree relative; 86% of patients were prescribed treatment with statins at most recent clinical visit	Myocardial infarction or angina	SMR for coronary heart disease indirectly standardized by age, sex, and calendar period rates in Britain and Wales	Males aged 0–79 years: SMR = 2.6 (95% CI: 1.7, 3.8)**; females aged 0–79 years: SMR = 3.7 (95% CI: 2.3, 5.8)**	The Simon Broome Register Group, 1999 (45)

* $p < 0.001$; ** $p < 0.0001$.

† FH, familial hypercholesterolemia; PMR, proportional mortality ratio; CI, confidence interval; TC, total cholesterol; SMR, standardized mortality ratio.

general population of England and Wales. Again, indirect standardization showed an increase in the number of deaths due to coronary heart disease for both males (SMR = 2.6, 95 percent CI: 1.7, 3.8) and females (SMR = 3.7, 95 percent CI: 2.3, 5.8) (45). The large size of this study allowed determination of age-specific mortality rates. The absolute risk of

coronary heart disease increased with age (45) and, notably, a large relative risk of fatal coronary heart disease was seen in young adults. For the 1980–1995 follow-up, an over 100-fold increase in risk for females (SMR = 125.00, 95 percent CI: 15.1, 451.3) and almost 50-fold increase for males (SMR = 48.4, 95 percent CI: 17.8, 105.5) were reported (45). In contrast, the relative risk in the same time period for persons aged 60–75 years was only 2.6 (95 percent CI: 1.3, 4.5) for females and 1.1 (95 percent CI: 0.5, 2.3) for males (45). This demonstrates a decrease in the relative risk of fatal coronary heart disease with increasing age.

Further, the time frame of the Simon Broome study overlaps with the introduction of statins in the early 1990s, allowing a comparison of standard mortality rates before and after the widespread use of these medications. The relative risk of coronary mortality in patients aged 20–59 years was higher from 1980 to 1991 (SMR = 8.0, 95 percent CI: 4.8, 12.6) than from 1992 to 1995 (SMR = 3.7, 95 percent CI: 1.6, 7.2) (45), suggesting that treatment is effective in lowering the risk of death from coronary disease in patients with clinical FH.

Family studies comparing all-cause standardized mortality ratios

Two studies by Sijbrands et al. (46, 47) examined all-cause mortality standardized mortality ratios for relatives of FH individuals, indirectly standardized to the age-, sex-, and calendar period-specific mortality rates of the general Dutch population. The pool of relatives studied combined approximately 50 percent affected and 50 percent unaffected individuals, so the reported standardized mortality ratio is an underestimate of the effect of the FH mutations. The first study traced 855 first-degree relatives of 113 unrelated patients (47). The authors observed an increased risk for all-cause mortality (SMR = 1.34, 95 percent CI: 1.16, 1.55). Similar to the Simon Broome Register, no excess mortality was found in older FH individuals (patients aged 80–103 years: SMR = 0.96, 95 percent CI: 0.60, 1.46). The design of the study allowed a comparison of the all-cause mortality standardized mortality ratio among families where FH was in part ascertained by premature onset of coronary heart disease and among families without coronary heart disease. An increased relative risk of death was observed in the premature coronary heart disease families (SMR = 1.46, 95 percent CI: 1.09, 1.94). This finding motivated the second study (46) in which Dutch records were used to trace the ancestry of three selected probands with the same mutation. A common ancestor pair living in 1830 was identified, and all living descendants of that pair were screened for the *V408M* mutation. A total of 412 individuals were found over eight generations of the transmission lines of the mutation, 250 of whom lived for at least 20 years. The overall relative risk for the 250 individuals (50 percent affected) was 1.32 (95 percent CI: 1.03, 1.67). Since these 250 identified individuals were not selected on the basis of clinical manifestations of FH, they better represent the natural course of FH, free from selection from cardiovascular disease. The level of excess mortality varied over time. There was no excess mortality in the 19th and early 20th centuries. The standardized mortality ratio then reached a peak between 1935 and 1964 (SMR = 1.78, 95 percent CI: 1.13, 2.76) and declined in the latter half of the 20th century. Taken together, these family studies show that selecting patients based on only clinical manifestations may overestimate mortality risk and that strong environmental factors may influence the increased mortality in patients with FH.

These results also complement earlier family studies of FH. A series of analyses based on survivors of myocardial infarction and their families in the United States in the 1970s by Goldstein et al. (48) and Hazzard et al. (49) found a high prevalence (3 percent) of heterozygous FH among survivors of myocardial infarction. Similar estimates (5 percent) were provided from the United Kingdom in 1972 by Patterson and Slack (50). In 1986, Williams et al. (51) screened 77 heterozygous FH members of four Utah pedigrees. They found that all 26 males born in the last two generations surveyed (after 1900) had coronary disease. In contrast, only one of five males born in the 19th century had coronary heart disease before the age of 60 years, providing additional evidence that environmental factors influence the association between clinical FH and coronary heart disease.

Allele-specific associations

Web table 2 and Web table 3 summarize studies that have examined the association between phenotypic outcomes and specific mutations in *LDLR* and *APOB*, respectively. The studies of *LDLR* mutations and coronary heart disease are among subjects with FH and/or their relatives, while the *APOB* studies are population-based case-control studies. It is worth noting that these studies differ in terms of their definition and methods of ascertainment of coronary heart disease. It may be the case that some mutations are associated with specific clinical manifestations of coronary heart disease, and variation in the coronary heart disease severity across studies limits the generalizability of the results.

Because of the large number of allelic variants, *LDLR* mutations are classified into two groups: 1) receptor-negative alleles and 2) receptor-defective alleles. However, there can be variation within these groups. For example, mutations in repeat 5 of the binding domain, which are coded by exon 4, have been shown to be associated with a more severe phenotype than other receptor-defective mutations (52). When possible, we have included comparisons of lipid levels with control (53, 54), unaffected relative (41), or normolipidemic (55) subjects in Web table 2, because LDL cholesterol levels and coronary heart disease prevalence in the general population vary by geographic location.

The effects of specific mutations can most easily be compared within founder populations in which a small number of alleles are responsible for the clinical FH phenotype. For example, a study in the Afrikaner populations shows a more severe phenotype, in terms of both lipid levels and coronary heart disease outcomes, for *V408M*, a receptor-negative mutation, than for *D206E*, a receptor-defective mutation (56). Similarly, studies of French Canadians are able to compare FH subjects who have primarily a 15-kilobase, receptor-negative deletion with those who have primarily the *W66G* receptor-defective mutation (54, 55).

However, because of their common origin, the FH heterozygotes in these populations may share other genetic or environmental factors, and these potential confounding factors may spuriously inflate the observed association (52).

Observational studies of small numbers of families or individuals have also noted additional *LDLR* alleles with atypically mild (57–62) or atypically severe (63, 64) phenotypes; however, the results of these studies may not be applicable to the general population.

To have large enough samples for phenotypic comparisons, studies in nonfounder populations have grouped *LDLR* mutations. Typically, mutations are grouped by either class, as was done in England and Wales (52), Italy (65), Norway (66), and Spain (67), or mutation type, as was done in Northern Ireland (68). As in the founder populations, these studies typically find LDL cholesterol levels and risk of cardiac death to be higher in individuals with receptor-negative alleles than in those with receptor-defective alleles (Web table 2). These results are supported by additional studies that have reported increased cholesterol levels for null alleles, but they did not ascertain coronary heart disease risk (69, 70). It has been noted (47) that the patient populations for many of these studies were selected from lipid clinics and, therefore, may have other environmental or familial factors that predisposed them to coronary heart disease. To address this issue, the Dutch national screening program for FH identified first-degree relatives of FH patients who were carriers of *LDLR* mutations, many of whom did not have clinical signs of FH. This program further identified relatives of these carriers who also had *LDLR* mutations. The index cases were then excluded from analysis to minimize the number of FH subjects ascertained through clinical manifestations of coronary heart disease (41). As in the other studies, receptor-negative alleles were found to be associated with a more severe phenotype than were receptor-defective alleles. This difference was due to primarily a particularly mild phenotype in the receptor-defective allele *N534H/2393del9* (41).

Case-control studies in Denmark (71) and the United States (72) have shown the *APOB R3500Q* allele to be associated with coronary heart disease, while a study in France (73) had inconclusive results (Web table 3). In the latter study, two of 622 cases and one of 639 controls were found to carry the *R3500Q* mutation; however, further analysis showed the control to have a history of coronary heart disease also. There is no evidence for an association between the *R3531C* allele and either coronary heart disease (71, 72) or hyperlipidemia (71, 72, 74). Association studies of the *R3500W* allele have not been practical because of the low frequency of the mutation in FH heterozygotes in Western populations (75–77). The *R3500Q* mutation results, on average, in a phenotype that is slightly more mild than that caused by mutations in *LDLR* (78–80). The clinical phenotype associated with *APOB* mutations is termed "familial defective apolipoprotein B-100" or "FDB." Recent work indicates that LDL cholesterol plasma levels may be lower in subjects with *APOB* mutations than in subjects with *LDLR* mutations, because of decreased intermediate-density lipoprotein to LDL transfer (81). However, there is a large overlap in cholesterol distributions for individuals with *LDLR* mutations compared with individuals with *APOB* mutations. As a result, familial defective apolipoprotein B-100 is generally considered to be clinically indistinguishable from FH (82).

INTERACTIONS

The phenotypic expression of heterozygous FH is quite variable, and at least part of this variation is due to the underlying molecular heterogeneity of the disease. Some studies demonstrate that age of onset of coronary heart disease clusters within families (39); however, phenotypic variation is still observed in families or populations sharing the same *LDLR* or *APOB* mutation (56, 83, 84), indicating that the clinical FH phenotype is influenced by additional environmental and/or genetic risk factors as well.

Gene-environment interactions

As noted above, multigenerational family studies demonstrate that the association of heterozygous FH with excess cardiovascular mortality varies over time. Specifically, studies by Sijbrands et al. (46) and Williams et al. (51) both noted a later onset of coronary heart disease mortality for FH heterozygotes in the 1900s compared with their 20th century descendants. Both studies propose that this mortality change is most likely due to changes in the environment, specifically an increase in dietary fat and sedentary lifestyle. Smaller studies have also demonstrated intrafamilial variability (53, 84) among first-degree relatives sharing the same *LDLR* mutations.

This interaction with environmental factors is also illustrated by comparing the phenotypic expression of heterozygous FH geographically (85). For example, total and LDL cholesterol levels in FH heterozygotes of similar genetic background vary in different parts of the world (86–88), even after controlling for differences in the underlying mutation. Pimstone et al. (89) matched Chinese FH subjects in Canada to FH heterozygotes in China with similar *LDLR* mutations. The subjects residing in Canada had higher concentrations of LDL cholesterol and an increased prevalence of tendinous xanthomata and coronary heart disease. Pereira et al. (90) examined FH heterozygotes in three Cuban families of Spanish descent in which one third of family members carried the *LDLR V408M* mutation common in the Afrikaner population. Although all the subjects had elevated LDL cholesterol, cardiovascular complications were rarely observed in the Cuban subjects compared with Afrikaners.

Several standard coronary risk factors have been shown to be associated with increased coronary risk in FH heterozygotes (69, 91–93). As in non-FH patients, sex and age are strong predictors of risk (3, 92) as are obesity (94, 95), diabetes (92, 96, 97), lipid levels (91, 98, 99), and smoking (91, 92, 96). However, these studies have examined only FH individuals and have not included non-FH individuals as controls; therefore, it is not clear that there is a gene-environment interaction for any of these risk factors. Instead, they may just be additive effects, with the increase in risk for individuals with FH being equivalent to the increased risk observed in the general population.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The association between clinical FH and coronary heart disease is well established, and there is evidence that receptor-negative mutations result in a more severe phenotype than do receptor-defective mutations. Further research in this field should focus on clarifying the genotype-phenotype relation and on understanding the impact of statins and other forms of treatment on reducing cardiovascular disease risk in individuals with *LDLR* or *APOB* mutations.

In addition, preliminary research indicates that the heterozygous FH phenotype is influenced by not only mutations in *LDLR* and *APOB* but also other genetic and environmental factors. However, it is not clear if these are synergistic interactions or simply additive effects of traditional coronary heart disease risk factors. These questions would best be answered by well-designed epidemiologic studies that include a control group of non-FH individuals.

ACKNOWLEDGMENTS

This project was supported under a cooperative agreement from the Centers for Disease Control and Prevention through the Association of Schools of Public Health (grants U36/CCU300430-20 and U36/CCU300430-22). This research was also supported by National Institutes of Health grant HL-49513 from the National Heart, Lung, and Blood Institute. S. E. H. is supported by the British Heart Foundation and in part by a grant from the Department of Health and Departments of Trade and Industry to the London Genetics Knowledge Park. R. L. Z. is supported by funding from the Departments of Health and of Trade and Industry, through the Cambridge Genetics Knowledge Park, and by the Wellcome Trust.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Association of Schools of Public Health.

REFERENCES

1. Müller C. Xanthomata, hypercholesterolemia, angina pectoris. Acta Med Scand 1938;89:75–84.
2. Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004;160:407–420.
3. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Sly WS, Childs B, et al, eds. The metabolic and molecular bases of inherited disease. New York, NY: McGraw-Hill Companies, Inc, 2001:2863–914.
4. Goldstein JL, Brown MS. Binding and degradation of low density lipoproteins by cultured human fibroblasts. Comparison of cells from a normal subject and from a patient with homozygous familial hypercholesterolemia. J Biol Chem 1974;249:5153–62.
5. Brown MS, Goldstein JL. Expression of the familial hypercholesterolemia gene in heterozygotes: mechanism for a dominant disorder in man. Science 1974;185:61–3.
6. Lindgren V, Luskey KL, Russell DW, et al. Human genes involved in cholesterol metabolism: chromosomal mapping of the loci for the low density lipoprotein receptor and 3-hydroxy-3-methylglutaryl-coenzyme A reductase with cDNA probes. Proc Natl Acad Sci U S A 1985;82:8567–71.
7. Heath KE, Day IN, Humphries SE. Universal primer quantitative fluorescent multiplex (UPQFM) PCR: a method to detect major and minor rearrangements of the low density lipoprotein receptor gene. J Med Genet 2000;37:272–80.
8. Villeger L, Abifadel M, Allard D, et al. The UMD-*LDLR* database: additions to the software and 490 new entries to the database. Hum Mutat 2002;20:81–7.
9. Knott TJ, Rall SC Jr, Innerarity TL, et al. Human apolipoprotein B: structure of carboxyl-terminal domains, sites of gene expression, and chromosomal localization. Science 1985;230:37–43.
10. Law SW, Lackner KJ, Hospattankar AV, et al. Human apolipoprotein B-100: cloning, analysis of liver mRNA, and assignment of the gene to chromosome 2. Proc Natl Acad Sci U S A 1985;82:8340–4.
11. Innerarity TL, Mahley RW, Weisgraber KH, et al. Familial defective apolipoprotein B-100: a mutation of apolipoprotein B that causes hypercholesterolemia. J Lipid Res 1990;31:1337–49.
12. Abifadel M, Varret M, Rabes JP, et al. Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154–6.
13. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat 1992;1:445–66.
14. Heath KE, Gahan M, Whittall RA, et al. Low-density lipoprotein receptor gene (*LDLR*) world-wide website in familial hypercholesterolaemia: update, new features and mutation analysis. Atherosclerosis 2001;154:243–6.
15. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003;24:1601–10.
16. Heart and stroke facts. Dallas, TX: American Heart Association, 2001.
17. Doll R, Hill AB. Mortality of British doctors in relation to smoking: observations on coronary thrombosis. Natl Cancer Inst Monogr 1966;19:205–68.
18. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986;256:2835–8.
19. Kardia SL, Modell SM, Peyser PA. Family-centered approaches to understanding and preventing coronary heart disease. Am J Prev Med 2003;24:143–51.
20. Hawe E, Talmud PJ, Miller GJ, et al. Family history is a coronary heart disease risk factor in the Second Northwick Park Heart Study. Ann Hum Genet 2003;67:97–106.
21. Eichner JE, Dunn ST, Perveen G, et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002;155:487–95.
22. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 1988;8:1–21.
23. Wilson PW, Schaefer EJ, Larson MG, et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol 1996;16:1250–5.
24. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–15.
25. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26.
26. Regnstrom J, Nilsson J, Tornvall P, et al. Susceptibility to low-density lipoprotein oxidation and coronary atherosclerosis in man. Lancet 1992;339:1183–6.

27. Libby P. Vascular biology of atherosclerosis: overview and state of the art. Am J Cardiol 2003;91:3A–6A.
28. Henney AM, Wakeley PR, Davies MJ, et al. Localization of stromelysin gene expression in atherosclerotic plaques by in situ hybridization. Proc Natl Acad Sci U S A 1991;88:8154–8.
29. Marks D, Thorogood M, Neil HA, et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003;168:1–14.
30. Huxley RR, Hawkins MH, Humphries SE, et al. Risk of fatal stroke in patients with treated familial hypercholesterolemia: a prospective registry study. Stroke 2003;34:22–5.
31. Kroon AA, Ajubi N, van Asten WN, et al. The prevalence of peripheral vascular disease in familial hypercholesterolaemia. J Intern Med 1995;238:451–9.
32. Descamps OS, Gilbeau JP, Leysen X, et al. Impact of genetic defects on atherosclerosis in patients suspected of familial hypercholesterolaemia. Eur J Clin Invest 2001;31:958–65.
33. Hutter CM, Austin MA, Humphries SE. Familial hypercholesterolemia, peripheral arterial disease, and stroke: a HuGE minireview. Am J Epidemiol 2004;160:430–5.
34. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet 1969;2:1380–2.
35. Stone NJ, Levy RI, Fredrickson DS, et al. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974;49:476–84.
36. Mabuchi H, Koizumi J, Shimizu M, et al. Development of coronary heart disease in familial hypercholesterolemia. Circulation 1989;79:225–32.
37. Gagne C, Moorjani S, Brun D, et al. Heterozygous familial hypercholesterolemia. Relationship between plasma lipids, lipoproteins, clinical manifestations and ischaemic heart disease in men and women. Atherosclerosis 1979;34:13–24.
38. Beaumont V, Jacotot B, Beaumont JL. Ischaemic disease in men and women with familial hypercholesterolaemia and xanthomatosis. A comparative study of genetic and environmental factors in 274 heterozygous cases. Atherosclerosis 1976;24:441–50.
39. Heiberg A, Berg K. The inheritance of hyperlipoproteinaemia with xanthomatosis. A study of 132 kindreds. Clin Genet 1976;9:203–33.
40. Kalina A, Csaszar A, Czeizel AE, et al. Frequency of the *R3500Q* mutation of the apolipoprotein B-100 gene in a sample screened clinically for familial hypercholesterolemia in Hungary. Atherosclerosis 2001;154:247–51.
41. Umans-Eckenhausen MA, Sijbrands EJ, Kastelein JJ, et al. Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population. Circulation 2002;106:3031–6.
42. Jensen J, Blankenhorn DH, Kornerup V. Coronary disease in familial hypercholesterolemia. Circulation 1967;36:77–82.
43. Mabuchi H, Miyamoto S, Ueda K, et al. Causes of death in patients with familial hypercholesterolemia. Atherosclerosis 1986;61:1–6.
44. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303:893–6.
45. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. Atherosclerosis 1999;142:105–12.
46. Sijbrands EJ, Westendorp RG, Defesche JC, et al. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. BMJ 2001;322:1019–23.
47. Sijbrands EJ, Westendorp RG, Paola Lombardi M, et al. Additional risk factors influence excess mortality in heterozygous familial hypercholesterolaemia. Atherosclerosis 2000;149:421–5.
48. Goldstein JL, Schrott HJ, Hazzard WR, et al. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. J Clin Invest 1973;52:1544–68.
49. Hazzard WR, Goldstein JL, Schrott MG, et al. Hyperlipidemia in coronary heart disease. 3. Evaluation of lipoprotein phenotypes of 156 genetically defined survivors of myocardial infarction. J Clin Invest 1973;52:1569–77.
50. Patterson D, Slack J. Lipid abnormalities in male and female survivors of myocardial infarction and their first-degree relatives. Lancet 1972;1:393–9.
51. Williams RR, Hasstedt SJ, Wilson DE, et al. Evidence that men with familial hypercholesterolemia can avoid early coronary death. An analysis of 77 gene carriers in four Utah pedigrees. JAMA 1986;255:219–24.
52. Gudnason V, Day IN, Humphries SE. Effect on plasma lipid levels of different classes of mutations in the low-density lipoprotein receptor gene in patients with familial hypercholesterolemia. Arterioscler Thromb 1994;14:1717–22.
53. Kotze MJ, Davis HJ, Bissbort S, et al. Intrafamilial variability in the clinical expression of familial hypercholesterolemia: importance of risk factor determination for genetic counselling. Clin Genet 1993;43:295–9.
54. Vohl MC, Gaudet D, Moorjani S, et al. Comparison of the effect of two low-density lipoprotein receptor class mutations on coronary heart disease among French-Canadian patients heterozygous for familial hypercholesterolaemia. Eur J Clin Invest 1997;27:366–73.
55. Gaudet D, Vohl MC, Couture P, et al. Contribution of receptor negative versus receptor defective mutations in the LDL-receptor gene to angiographically assessed coronary artery disease among young (25–49 years) versus middle-aged (50–64 years) men. Atherosclerosis 1999;143:153–61.
56. Kotze MJ, De Villiers WJ, Steyn K, et al. Phenotypic variation among familial hypercholesterolemics heterozygous for either one of two Afrikaner founder LDL receptor mutations. Arterioscler Thromb 1993;13:1460–8.
57. Castillo S, Reyes G, Tejedor D, et al. A double mutant [*N543H+2393del9*] allele in the LDL receptor gene in familial hypercholesterolemia: effect on plasma cholesterol levels and cardiovascular disease. (Mutation in brief). Hum Mutat 2002;20:477.
58. Arca M, Jokinen E. Low density lipoprotein receptor mutations in a selected population of individuals with moderate hypercholesterolemia. Atherosclerosis 1998;136:187–94.
59. Slimane MN, Lestavel S, Sun X, et al. *Fh-Souassi*: a founder frameshift mutation in exon 10 of the LDL-receptor gene, associated with a mild phenotype in Tunisian families. Atherosclerosis 2001;154:557–65.
60. Vuorio AF, Aalto-Setala K, Koivisto UM, et al. Familial hypercholesterolaemia in Finland: common, rare and mild mutations of the LDL receptor and their clinical consequences. Finnish FH-group. Ann Med 2001;33:410–21.
61. Sun XM, Neuwirth C, Wade DP, et al. A mutation (*T-45C*) in the promoter region of the low-density-lipoprotein (LDL)-receptor gene is associated with a mild clinical phenotype in a patient with heterozygous familial hypercholesterolaemia (FH). Hum Mol Genet 1995;4:2125–9.
62. Koivisto PV, Koivisto UM, Kovanen PT, et al. Deletion of exon 15 of the LDL receptor gene is associated with a mild form of familial hypercholesterolemia. *FH-Espoo*. Arterioscler Thromb 1993;13:1680–8.
63. Sun XM, Patel DD, Bhatnagar D, et al. Characterization of a splice-site mutation in the gene for the LDL receptor associated with an unpredictably severe clinical phenotype in English patients with heterozygous FH. Arterioscler Thromb Vasc Biol

1995;15:219–27.
64. Widhalm K, Iro C, Lindemayr A, et al. Heterozygous familial hypercholesterolemia: a new point-mutation (*1372del2*) in the LDL-receptor gene which causes severe hypercholesterolemia. (Mutation and polymorphism report). Hum Mutat 1999;14:357.
65. Bertolini S, Cantafora A, Averna M, et al. Clinical expression of familial hypercholesterolemia in clusters of mutations of the LDL receptor gene that cause a receptor-defective or receptor-negative phenotype. Arterioscler Thromb Vasc Biol 2000;20:E41–52.
66. Tonstad S, Leren TP, Sivertsen M, et al. Determinants of lipid levels among children with heterozygous familial hypercholesterolemia in Norway. Arterioscler Thromb Vasc Biol 1995;15: 1009–14.
67. Chaves FJ, Real JT, Garcia-Garcia AB, et al. Large rearrangements of the LDL receptor gene and lipid profile in a FH Spanish population. Eur J Clin Invest 2001;31:309–17.
68. Graham CA, McClean E, Ward AJ, et al. Mutation screening and genotype:phenotype correlation in familial hypercholesterolaemia. Atherosclerosis 1999;147:309–16.
69. Jensen HK. The molecular genetic basis and diagnosis of familial hypercholesterolemia in Denmark. Dan Med Bull 2002;49:318–45.
70. Sun XM, Patel DD, Knight BL, et al. Comparison of the genetic defect with LDL-receptor activity in cultured cells from patients with a clinical diagnosis of heterozygous familial hypercholesterolemia. The Familial Hypercholesterolaemia Regression Study Group. Arterioscler Thromb Vasc Biol 1997;17:3092–101.
71. Tybjaerg-Hansen A, Steffensen R, Meinertz H, et al. Association of mutations in the apolipoprotein B gene with hypercholesterolemia and the risk of ischemic heart disease. N Engl J Med 1998; 338:1577–84.
72. Ludwig EH, Hopkins PN, Allen A, et al. Association of genetic variations in apolipoprotein B with hypercholesterolemia, coronary artery disease, and receptor binding of low density lipoproteins. J Lipid Res 1997;38:1361–73.
73. Brousseau T, Arveiler D, Cambou JP, et al. Familial defective apolipoprotein B-100 and myocardial infarction. The ICTIM Study. Atherosclerosis 1995;116:269–71.
74. Rabes JP, Varret M, Devillers M, et al. *R3531C* mutation in the apolipoprotein B gene is not sufficient to cause hypercholesterolemia. Arterioscler Thromb Vasc Biol 2000;20:E76–82.
75. Tybjaerg-Hansen A, Gallagher J, Vincent J, et al. Familial defective apolipoprotein B-100: detection in the United Kingdom and Scandinavia, and clinical characteristics of ten cases. Atherosclerosis 1990;80:235–42.
76. Talmud PJ, Tamplin OJ, Heath K, et al. Rapid testing for three mutations causing familial defective apolipoprotein B-100 in 562 patients with familial hypercholesterolaemia. Atherosclerosis 1996;125:135–7.
77. Loggen U, Boden A, Baron H, et al. Apolipoprotein B-100 gene mutations and cholesterol control in German patients. Atherosclerosis 2003;166:411–12.
78. Pimstone SN, Defesche JC, Clee SM, et al. Differences in the phenotype between children with familial defective apolipoprotein B-100 and familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1997;17:826–33.
79. Hansen PS, Defesche JC, Kastelein JJ, et al. Phenotypic variation in patients heterozygous for familial defective apolipoprotein B (FDB) in three European countries. Arterioscler Thromb Vasc Biol 1997;17:741–7.
80. Miserez AR, Keller U. Differences in the phenotypic characteristics of subjects with familial defective apolipoprotein B-100 and familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1995;15:1719–29.
81. Gaffney D, Forster L, Caslake MJ, et al. Comparison of apolipoprotein B metabolism in familial defective apolipoprotein B and heterogeneous familial hypercholesterolemia. Atherosclerosis 2002;162:33–43.
82. Defesche JC, Pricker KL, Hayden MR, et al. Familial defective apolipoprotein B-100 is clinically indistinguishable from familial hypercholesterolemia. Arch Intern Med 1993;153:2349–56.
83. Roy M, Sing CF, Betard C, et al. Impact of a common mutation of the LDL receptor gene, in French-Canadian patients with familial hypercholesterolemia, on means, variances and correlations among traits of lipid metabolism. Clin Genet 1995;47:59–67.
84. Levy E, Minnich A, Cacan SL, et al. Association of an exon 3 mutation (*Trp66–>Gly*) of the LDL receptor with variable expression of familial hypercholesterolemia in a French Canadian family. Biochem Mol Med 1997;60:59–69.
85. Hegele RA. Environmental modulation of atherosclerosis end points in familial hypercholesterolemia. Atheroscler Suppl 2002; 2:5–7.
86. Thompson GR, Seed M, Niththyananthan S, et al. Genotypic and phenotypic variation in familial hypercholesterolemia. Arteriosclerosis 1989;9:I75–80.
87. Sun XM, Patel DD, Webb JC, et al. Familial hypercholesterolemia in China. Identification of mutations in the LDL-receptor gene that result in a receptor-negative phenotype. Arterioscler Thromb 1994;14:85–94.
88. Slimane MN, Pousse H, Maatoug F, et al. Phenotypic expression of familial hypercholesterolaemia in central and southern Tunisia. Atherosclerosis 1993;104:153–8.
89. Pimstone SN, Sun XM, du Souich C, et al. Phenotypic variation in heterozygous familial hypercholesterolemia: a comparison of Chinese patients with the same or similar mutations in the LDL receptor gene in China or Canada. Arterioscler Thromb Vasc Biol 1998;18:309–15.
90. Pereira E, Ferreira R, Hermelin B, et al. Recurrent and novel LDL receptor gene mutations causing heterozygous familial hypercholesterolemia in La Habana. Hum Genet 1995;96:319–22.
91. Hill JS, Hayden MR, Frohlich J, et al. Genetic and environmental factors affecting the incidence of coronary artery disease in heterozygous familial hypercholesterolemia. Arterioscler Thromb 1991;11:290–7.
92. Hopkins PN, Stephenson S, Wu LL, et al. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2001;87:547–53.
93. Jansen AC, van Wissen S, Defesche JC, et al. Phenotypic variability in familial hypercholesterolaemia: an update. Curr Opin Lipidol 2002;13:165–71.
94. Gaudet D, Vohl MC, Perron P, et al. Relationships of abdominal obesity and hyperinsulinemia to angiographically assessed coronary artery disease in men with known mutations in the LDL receptor gene. Circulation 1998;97:871–7.
95. Watts GF, Barrett PH. High-density lipoprotein metabolism in familial hypercholesterolaemia: significance, mechanisms, therapy. Nutr Metab Cardiovasc Dis 2002;12:36–41.
96. Vuorio AF, Turtola H, Piilahti KM, et al. Familial hypercholesterolemia in the Finnish north Karelia. A molecular, clinical, and genealogical study. Arterioscler Thromb Vasc Biol 1997;17:3127–38.
97. Yanagi K, Yamashita S, Kihara S, et al. Characteristics of coronary artery disease and lipoprotein abnormalities in patients with heterozygous familial hypercholesterolemia associated with diabetes mellitus or impaired glucose tolerance. Atherosclerosis 1997;132:43–51.
98. Smilde TJ, van Wissen S, Wollersheim H, et al. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184–95.
99. Real JT, Chaves FJ, Martinez-Uso I, et al. Importance of HDL cholesterol levels and the total/HDL cholesterol ratio as a risk factor for coronary heart disease in molecularly defined heterozygous familial hypercholesterolaemia. Eur Heart J 2001;22:465–71.