

Familial hypercholesterolemia and coronary heart disease: a HuGE association review

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Introduction

Familial hypercholesterolemia (FH) occurs with a frequency of 1 in 500 in the Caucasian population. It is characterised by autosomal inheritance of increased cholesterol and LDL cholesterol levels. This is consistently associated with increased coronary heart disease (CHD) risk. The majority of FH causing mutations have been identified in the LDLR gene although mutations have also been found in APOB and PCSK9.

Issue addressed in paper

Several previous studies were analysed to examine the association between FH and CHD:

1. *Studies estimating the cumulative probability of CHD:* Association studies in the UK, US and other countries determined there was a high risk of premature CHD among patients with clinical FH.
2. *Cohort studies of standardized mortality rates for CHD and all-cause mortality:* A range of international studies have shown that there is a) a high prevalence of early CHD in FH patients b) elevated standardised mortality ratios of observed: expected deaths in both sexes c) an increased number of deaths in FH affected relatives compared to the general population d) a large risk of fatal CHD in young adults with FH and e) a lowered risk of death from CHD if the FH patient is treated with statins.
3. *Family studies comparing all-cause standardized mortality ratios:* Analysis of family studies show an increased risk in all-cause mortality amongst FH relatives. In addition environmental factors were shown to influence the association between clinical FH and CHD.
4. *Allele specific associations:* LDLR mutations can be classified as either receptor negative or receptor defective according to their effect on LDLR protein function although there can be variation within these groups. Studies in non founder populations have shown a more severe FH phenotype is associated with individuals with receptor negative mutations. The clinical phenotype associated with APOB mutations is termed "familial defective apolipoprotein B-100 (FDB) which is considered to be clinically indistinguishable from FH.

Summary of findings

Phenotypic expression of heterozygous FH is quite variable due to molecular heterogeneity and additional environmental or genetic risk factors. These are thought to include sex, age, obesity, diabetes and lipid levels. It is not clear if these are synergistic interactions or additive effects of traditional CHD risk factors.

The paper concluded that the association between clinical FH and CHD is well established. Further study is required to clarify genotype-phenotype associations and the efficacy of treatments such as statins in reducing CHD risk.