Genetics of Familial Combined Hyperlipidemia

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Complex disorders are caused by several environmental factors that interact with multiple genes. These diseases are common at the population level and constitute a major health problem in Western societies. Familial combined hyperlipidemia (FCHL) is characterized by elevated levels of serum total cholesterol, triglycerides, or both. This disorder is estimated to be common in Western populations with a prevalence of 1% to 2%. In addition, 14% of patients with premature coronary heart disease (CHD) have FCHL, making this disorder one of the most common genetic dyslipemias underlying premature CHD. Both genetic and environmental factors are suggested to affect the complex FCHL phenotype, but no specific susceptibility genes to FCHL have been identified. It is hoped that further analysis of the first FCHL locus and other new loci obtained in genome-wide scans will guide us to genes predisposing to this complex disorder.

Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCHL) is a common familial dyslipidemia predisposing to premature coronary heart disease (CHD) [1–6,7••]. Despite intensive research to reveal the molecular mechanisms causing FCHL, the cause of FCHL remains unknown. Consequently, a significant number of affected individuals without proper prevention and care are exposed to premature CHD. Thus, the diagnosis in a single patient cannot be based on any FCHL-specific metabolic or genetic marker but on tedious family studies.

The genetic component in FCHL is suggested by familial aggregation of dyslipidemia, such as the Fredrikson’s combined hyperlipidemia phenotype IIb, which occurs six times more commonly in the first-degree relatives of FCHL probands than in the controls [2]. In addition, segregation studies have presented evidence for major genes affecting serum triglycerides (TGs) [8] and apolipoprotein (apoB) [9], and an FCHL-related phenotype, small dense low-density lipoprotein (LDL) [10]. A recent study also supported a major gene having pleiotropic effects on both LDL particle size and apoB levels [11].

The FCHL phenotype is characterized by elevated serum total cholesterol (TC) levels (Fredrikson’s lipid phenotype type IIa), elevated TG levels (type IV), or both (type IIb) in affected family members [1]. Further, increased apoB levels often are detected in affected family members [1,12]. Repeated lipid measurements also have indicated that affected individuals may change their lipid phenotype within a family [12]. Age- and sex-specific cut-points (the 90th or 95th percentiles) for serum TC and TG levels commonly are used to define the lipid phenotypes IIa, IV, and IIb for the FCHL diagnosis [1,13]. The FCHL diagnosis is made based on the presence of both combined hyperlipidemia and multiple type of hyperlipidemia (IIa, IIb, or IV) in relatives of the proband [13]. Less stringent FCHL criteria, such as the existence of two different kinds of lipid phenotypes in the family, lower percentile cut-points or lipid cut-points not representing any age-sex specific percentiles, also have been used [13–16]. In addition, elevated apoB levels or the existence of premature CHD often have been required in FCHL families, and in some studies LDL cholesterol has been used instead of serum TC [13]. Taken together, FCHL lacks commonly accepted unequivocal diagnostic criteria and the criteria selected seem to vary significantly between different study groups.

No definite metabolic defect has been identified in FCHL, although several metabolic pathways have been suggested to participate in FCHL pathophysiology [17]. An increased apoB concentration is a consistent metabolic finding in FCHL patients [4,18], and a defect in the metabolism of apoB-containing lipoproteins is thus possible. Conversely, prolonged postprandial lipemia and elevated serum concentrations of free fatty acids are detected among FCHL patients [19,20]. This would indicate a primary defect in lipid synthesis or lipolysis in adipose tissue [20]. Defects in glucose metabolism, such as insulin resistance and glucose intolerance [19,21••,22], also may contribute to FCHL. Further, the FCHL phenotype overlaps with several common disorders. These include hyperapobetalipoproteinemia, LDL subclass pattern B, familial dyslipidemic hypertension, non-insulin-dependent diabetes mellitus, and metabolic syndrome [13]. In summary, the current data suggest that most likely FCHL is a heteroge-
Genetic Mapping of Complex Diseases

In genetic mapping, the chromosomal localization of a gene is found by comparing the inheritance of the phenotype of a gene with the inheritance of a marker without knowing what the gene is. This strategy has been highly useful in mapping the chromosomal regions of monogenic diseases. Encouraged by this success, human geneticists have started to explore more common, "complex" traits in which no simple Mendelian inheritance can be revealed and in which both environmental and genetic factors interplay as predisposing factors for the disease [23].

Several factors limit the mapping of multifactorial complex diseases (Table 1). These parameters are difficult to monitor with the existing statistical tools. For example, an unknown mode of inheritance is typical for complex traits: the disease seems to be familial, but yet does not follow a Mendelian segregation. FCHL exemplifies this well. Although FCHL originally was suggested to be a dominant autosomal disorder [1], a more complex polygenic background is likely, as suggested by metabolic [17] and segregation studies [8,9]. In fact, it is commonly considered that inheritance patterns adopted for complex diseases in linkage analysis represent oversimplifications [23].

Another serious problem in mapping of complex traits is varying, equivocal criteria for a disease phenotype. Considering FCHL, it actually can be claimed that every study group uses criteria of its own for FCHL.

In genetic studies of complex traits, several possibilities exist to increase the likelihood of genetic involvement: families with multiple affected individuals, early-onset subjects, extreme phenotypes, and affected individuals originating from genetic isolates can be selected. Obvious environmental risk factors also should be excluded or standardized [23,24]. In addition, animal models are ideal tools to study complex diseases, providing that a well-defined animal model exists for the disease being investigated.

The genetic heterogeneity significantly disturbs statistical analyses of complex diseases. Therefore, study material sets collected from isolated populations commonly are used, although the advantages are predicted to be smaller than in monogenic diseases due to restricted linkage disequilibrium and common allelic variants in complex diseases. Isolated populations also seem to share relatively homogeneous environmental backgrounds compared with more mixed populations. This may turn out to be an important additional advantage. The isolated populations have, however, not yet proven their value in the final identification of genes in complex diseases. It is hoped that the high expectations will materialize in the form of isolation of some causative genes.

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**Table 1. Factors Confounding Genetic Mapping of Susceptibility Genes in Complex Diseases Such as Familial Combined Hyperlipidemia**

<table>
<thead>
<tr>
<th>Genetic heterogeneity</th>
<th>Reduced penetrance</th>
<th>Phenocopies</th>
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<tr>
<td>Diagnosis and classification of the phenotype</td>
<td>Unknown mode of inheritance</td>
<td>Common disease-predisposing alleles in the population</td>
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**Candidate Gene Approach in Familial Combined Hyperlipidemia**

The candidate gene strategy is used to test whether a genetic variation of a certain candidate gene predisposes to a disease. Various study types, including case/control-sets, affected sibling pairs, and multiplex families, can be used in this approach.

The most thoroughly studied FCHL candidate genes are the lipoprotein lipase (LPL) and the apolipoprotein A1C3A4 (apoA1C3A4) gene cluster, because of their central roles in lipid metabolism. LPL catalyzes the hydrolysis of TGs of very low-density lipoprotein (VLDL) and chylomicrons and thus delivers fatty acids to tissues. It has been shown that one third of FCHL subjects have decreased LPL activity [25], suggesting that the LPL mutations influencing catalytic activity could contribute to the lipid phenotype in FCHL and that a subset of FCHL patients may be heterozygotes for LPL mutations. However, several studies have implied that LPL mutations in the coding sequence or in the promoter do not represent common causes of FCHL [26,27] and an association and a linkage study provided negative results as well [28,29]. The LPL gene may still act as a minor or modifying gene in FCHL. This is supported by two studies [30,31] showing that common LPL mutations affect lipid phenotypes in FCHL subjects (Table 2). Other lipolytic enzymes, the hepatic lipase (HL) and hormone sensitive lipase (LPIE), also have been investigated in FCHL. Considering the HL gene, one preliminary association study showed a positive result [32], whereas a linkage study remained negative [29]. Neither was there any evidence for linkage between FCHL and the LPIE gene [29] (Table 2).

Genes of the apoA1C3A4 gene cluster participate in the metabolism of high-density lipoprotein (HDL) and TG-rich lipoprotein particles. Apolipoprotein C3 (apoC3) especially can be considered a relevant candidate gene for FCHL because of its important role as a regulator of plasma TG levels and as an LPL inhibitor. Originally, data by Hayden et al. [33] showed an association between FCHL and an Xmn1 RFLP in the 5' flanking region of the apolipoprotein A1 (apoA1) gene. This finding was further confirmed by linkage in seven FCHL families with probands of northern European origin [34]. In this study, the probands were required to have the X2 allele of the Xmn1 polymorphism in the apoA1 gene. Several associations between this

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**Note:**

Familial Combined Hyperlipidemia (FCHL) is a genetic disorder that involves a number of metabolic defects, and a combination of separate disorders with partly overlapping genetic and environmental components cannot be excluded.