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Familial occurrence of abnormalities of high-density lipoprotein cholesterol

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Abstract. In families, well-known monogenic high-density lipoprotein cholesterol (HDL-C) disorders characterized by extreme HDL-C levels on both ends of the continuum occur in multiple HDL pathways and can confer increased risk for atherosclerotic disease. Polygenic HDL-C variants have been more difficult to identify. In many family and twin studies in different populations, HDL-C levels have been shown to be highly heritable, explaining, on average, between 40% and 60% of between-individual variation. This review of abnormal HDL in families addresses known monogenic HDL disorders and HDL-C heritability in the general population, and presents novel data on the heritability of HDL-C in families with a history of premature coronary artery disease. We conclude that levels of HDL-C and HDL abnormalities are largely under genetic control and environmental and behavioral factors alone have only a modest impact. While rare, monogenic disorders offer considerable insight into the genetics of HDL regulation. Moderate to high heritability estimates across different family populations suggest that future genetic studies will be successful in identifying HDL genetic trait loci and that translational studies will ultimately lead to therapies that optimize the cardiovascular protective benefits of HDL.

Introduction

Studies have clearly established the role of low levels of HDL cholesterol (HDL-C) in increased risk for coronary artery disease (CAD), particularly related to premature familial-clustered CAD.[1,2] Although environmental factors play a modest role among the general population, variations in levels of HDL-C are explained largely by genetic factors.[3,4] Levels of HDL-C across the continuum appear to be highly heritable, explaining, on average, between 40% and 60% of the between-individual variation observed.[5–15] While lifestyle and environmental factors, such as diet, exercise, alcohol consumption, estrogen use, some medications, and smoking behavior, influence levels of HDL-C,[16–27] they are unlikely to influence the very-low HDL-C levels that appear to be causally linked to premature CAD in families.[3,28] Although HDL-C is strongly associated with a panoply of other inherited biological factors that also contribute to premature CAD in families, including obesity and components of the metabolic syndrome,[29] a considerable portion of intrafamilial clustering of HDL-C appears to be genetically determined.[30,31] In addition, isolated low HDL-C levels account for between 1% and 4% of familial-clustered premature CAD, suggesting that low HDL-C is not simply a marker for other high-risk bio-

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Table 1 Familial disorders affecting plasma high-density lipoprotein cholesterol concentrations*

Familial disorder	Gene defect	Inheritance pattern	Lipoprotein abnormalities	Clinical findings	CAD risk	Ref.
Reduced concentrations of HDL-C						
Familial hypoalphalipoproteinemia (ApoA-I deficiency)	ApoA-I gene mutations (several described) or unknown	Autosomal dominant (common to rare)	HDL-C 15-35 mg/dL ($<10^{th}$ %tile) and low ApoA-I with normal to mildly elevated triglycerides and normal LDL-C	Occasionally xanthomas and corneal opacities. Rare systemic amyloidosis.	Increased, premature	34,39,44
ApoA-I Milano (variant familial ApoA-I deficiency)	ApoA-I gene mutation	Autosomal dominant (rare)	Low HDL and ApoA-I with modest elevation in triglycerides and VLDL-C	Corneal opacities	Decreased	47–9
Familial LCAT deficiency (complete LCAT deficiency)	LCAT gene mutations (several described)	Autosomal recessive (rare)	HDL-C $<$10 mg/dL, low ApoA-I and variable high triglycerides and LDL-C	Corneal opacities, renal insufficiency, anemia, organomegaly	Increased, premature	39,44,52–55
Fish-eye disease (partial LCAT deficiency)	LCAT gene mutations	Autosomal recessive (rare)	HDL-C $<$10 mg/dL, low ApoA-I and variable high triglycerides and LDL-C	Progressive extreme corneal opacities and impaired vision	Variable reports	44,56,57
Tangier disease	ABCA-I gene mutations	Autosomal recessive (rare)	*Homozygotes:* HDL-C $<$10 mg/dL with low LDL-C and mildly elevated triglycerides *Heterozygotes:* moderately low HDL-C and ApoA-I	Hyperplastic orange tonsils and adenoids, neuropathy, organomegaly in some	Increased, premature	58–66
LPL deficiency	LPL gene mutations	Autosomal recessive (rare)	*Homozygotes:* Markedly decreased HDL-C and ApoA-1 with severe hypertriglyceridemia and chylomicronemia *Heterozygotes:* moderate decreased HDL with variable increases in total cholesterol, triglycerides, and VLDL	Severe hypertryglyceridemia associated with pancreatitis, eruptive xanthomas, hepatosplenomegaly	May be increased in some variants	39,67–78