Genetic Basis of Lipoprotein Disorders

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Lipoproteins are complexes of lipids and proteins that carry cholesterol in the bloodstream. They are spherical particles with a coat consisting principally of amphiphilic phospholipids and proteins, called apolipoproteins, and a core, which is essentially an oil droplet, consisting of varying proportions of triglycerides and cholesteryl esters. Lipoprotein levels are determined by genes that code for proteins that control lipoprotein synthesis, lipoprotein processing, and lipoprotein breakdown. These include the apolipoproteins, A-I, A-II, A-IV, B, CI, CII, CIII, D, E, and apo(a), the lipoprotein processing proteins, lipoprotein lipase (LPL),[1] hepatic triglyceride lipase (HTGL), lecithin cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP), and the lipoprotein receptors, LDL receptor, chylomicron remnant receptor, and scavenger receptor. The following is a brief summary of current knowledge about the genetic basis of lipoprotein disorders. Additional background information and references may be found in several recent review articles (1-11).

Since 1982, the genes for the 10 apolipoproteins, the 4 lipoprotein processing proteins, and the LDL receptor have all been isolated, sequenced, and mapped in the human genome. (For the primary reviews see references 1, 9, and 10.) Chromosomes 1, 2, 3, 6, and 8 harbor the A-II, B, D, apo(a), and LPL genes, respectively. Chromosome 11 contains a cluster of three apolipoprotein genes, A-I, CIII, and A-IV, all within a 20-kb DNA segment. Chromosome 15 contains the gene for HTGL. Two genes reside on chromosome 16, the CETP, and LCAT genes. Four genes reside on chromosome 19. The LDL receptor is on the short arm of chromosome 19 and a cluster of three apolipoprotein genes, E, CI, and CII, are on the long arm of chromosome 19 within a 50-kb DNA segment. The LDL receptor gene and the apolipoprotein genes on chromosome 19 are not linked (Fig. 1) (13). The structures of the lipoprotein transport genes have been analyzed and gene families identified. Seven of the apolipoprotein genes appear to be part of a gene family based on similarities in coding sequences as well as exon-intron organization. These are the A-I, A-II, A-IV, CI, CII, CIII, and E genes (1, 2, 8). The apo D gene appears to be similar to the gene for retinol-binding protein (14). The apo(a) gene is homologous with and closely linked to the plasminogen gene (15, 16), and the genes for LPL and HTGL appear to be quite similar (17).

This new information about the lipoprotein transport genes is being applied to understanding the genetic basis of lipoprotein disorders. The known genetic defects will now be discussed in terms of how they alter the lipoprotein transport pathways for exogenous and endogenous fats and a third pathway for the reverse transport of cholesterol from peripheral tissues to the liver.

Genetic defects in exogenous fat transport

In the normal exogenous fat transport pathway (Fig. 1), dietary triglycerides and cholesterol are processed in the intestinal lumen, absorbed, and packaged in the intestinal epithelial cell into large triglyceride-rich particles called chylomicrons that also contain cholesterol. Proteins, which make up 1% of the weight of the chylomicron, reside on the surface of the particle and consist of the intestinal form of apo B (B-48), apo A-I, and apo A-IV. In the circulation, chylomicrons acquire the C apolipoproteins, particularly apo CII, which is a required cofactor for the LPL enzyme. This enzyme resides on the capillary endothelium and hydrolyzes most of the core chylomicron triglycerides. During lipolysis excess surface components consisting of phospholipids and apolipoproteins are transferred to HDL and apo E is transferred from HDL to the now cholesteryl ester–enriched chylomicron remnant. These remnants are then efficiently cleared by hepatic receptors called chylomicron remnant receptors, which recognize apo E on their surface.

Genetic defects have been identified in exogenous fat transport (Table I). Defective chylomicron secretion is found in two conditions, abetalipoproteinemia and homozygous hypobetalipoproteinemia (12). These conditions occur with a frequency of less than one in one million in the population. They are characterized by an absence of apo B containing lipoproteins, including chylomicrons, VLDL and LDL. The inability to produce chylomicrons results in fat malabsorption and the ensuing fat soluble vitamin deficiency leads to ataxic neuropathy, retinitis pigmentosa, and a form of anemia characterized by acanthocytes. Both conditions are inherited in an autosomal recessive manner. However, in abetalipoproteinemia obligate heterozygote carriers have normal LDL cholesterol levels, whereas in homozygous hypobetalipoproteinemia carriers have 30–50% of normal levels. Linkage studies show that homozygous hypobetalipoproteinemia is due to defects in the apo B gene (18, 19), but abetalipoproteinemia is not (20, 21). The locus of the genetic abnormality in abetalipoproteinemia is not yet explained.

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1. *Abbreviations used in this paper:* CETP, cholesterol ester transfer protein; HTGL, hepatic triglyceride lipase; IDL, intermediate density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LPL, lipoprotein lipase.

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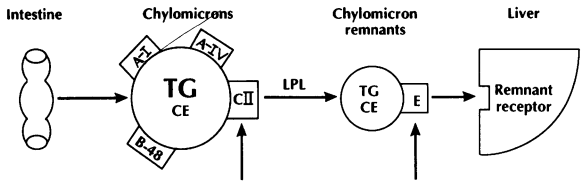

Figure 1. Exogenous fat transport pathway. Dietary fat is packaged in intestinal epithelial cells into chylomicrons. Chylomicrons are metabolized in a two-step process that includes hydrolysis of triglycerides by LPL to form chylomicron remnants and remnant uptake through recognition of apo E by an hepatic remnant receptor.

Two diseases that result in defective chylomicron processing are known, called LPL deficiency and apo CII deficiency (22–24). The frequency of these disorders is also less than one in one million. Both conditions are characterized by excess chylomicrons and VLDL. Other symptoms can include pancreatitis and eruptive xanthomas. The large chylomicrons that accumulate in this disorder appear not to be atherogenic and atherosclerosis susceptibility is not increased. The inheritance of LPL deficiency and apo CII deficiency is autosomal recessive and due to defects in the LPL and apo CII genes, respectively. Recently, defective LPL gene alleles due to insertions or deletions have been demonstrated (25). In addition, apo CII gene abnormalities caused by a splice site mutation and small deletions have been observed (26–28).

Chylomicron remnant clearance can also be defective. This is much more common in the population than chylomicron formation or processing defects because of common variation in the apo E gene (29, 30). This gene codes for the protein on the surface of the chylomicron remnant that is the ligand for receptor mediated clearance of this particle. There are three common alleles of the apo E gene in the population called E4, E3, and E2, and these result in six common phenotypes (29–31). One of the allele gene products, E2, fails to bind to receptors (32–34), and homozygotes and heterozygotes for E2 have defective chylomicron remnant clearance (35–37).

The apo E allele and phenotype frequencies in Caucasians have been determined in many studies (38). The E4 allele has a frequency of 15%, the E3 allele is the most common with a frequency of 77%, and the defective E2 allele has a frequency of 8%. This results in homozygous phenotype frequencies of E4/4, 2%; E3/3, 59%; and E2/2, 1%. The heterozygous phenotype frequencies are E4/3, 23%; E3/2, 12%; and E4/2, 2%. Thus, ~ 1% of the general population are homozygous for the defective apo E allele, E2, and have the E2/2 phenotype. Another 14% of the population are heterozygous for the defective E2 allele, and have the E3/2 and E4/2 phenotypes.

Table I. Defects in Exogenous Fat Transport

	Defect	Disease
Chylomicron secretion	Apo B	Hypobetalipoproteinemia Abetalipoproteinemia
Chylomicron processing	LPL	LPL deficiency
	Apo CII	Apo CII deficiency
Chylomicron remnant clearance	Apo E	Type III hyperlipoproteinemia

Apo E, a 299-amino acid polypeptide, is a ligand for both the chylomicron remnant and LDL receptors. The receptor binding region is between amino acids 140 and 160 (34, 39–41). The structural differences between E4, E3, and E2 have been determined (42). If one takes the most common allele E3 as wild type, the E4 allele represents a mutation of amino acid 112 cysteine to arginine. This mutation is not within the receptor binding domain and E4 binds receptors normally. E2 results from a mutation of amino acid 158 arginine to cysteine. This mutation causes a loss of a positive charge in the receptor binding region and E2 has only 1–2% of normal receptor binding activity (32–34).

Aside from the common genetic variations in the apo E polypeptide at residues 112 and 158, other rare apo E mutations have been identified (reviewed in reference 1). Several of these involve amino acid substitutions replacing positively charged with neutral amino acids in the apo E receptor binding region and they are defective in receptor binding (33, 43–45). This emphasizes the importance of the positively charged amino acid residues in the receptor binding domain that presumably interact with the negatively charged ligand binding domain of the LDL receptor (10). Finally, a rare form of type III hyperlipoproteinemia has been reported associated with apo E deficiency (46). The molecular defect appears to be a mutation in the splice acceptor site of the third intron of the apo E gene, causing an unstable mRNA (47).

Chylomicron remnant clearance is defective in three conditions. The first of these is type III hyperlipoproteinemia, which occurs in 1 in 5,000 individuals in the general population (48, 49). These patients have the E2/2 phenotype and present with elevated fasting levels of cholesterol and triglycerides due to the presence in fasting plasma of greatly elevated levels of chylomicron remnants and intermediate density lipoproteins (IDL). Type III hyperlipoproteinemic patients may have either low, normal, or elevated LDL cholesterol levels. They generally have xanthomas and frequently have coronary heart or peripheral vascular disease. A second condition with defective chylomicron clearance is the more common situation of individuals with the E2/2 phenotype who do not present with fasting hyperlipidemia (38, 50–52). Normolipidemic E2/2 individuals, who make up 1% of the population, have difficulty clearing chylomicron remnants from their bloodstream. However, in fasting plasma the increase in chylomicron remnants and IDL is offset by a great decrease in LDL cholesterol levels. These individuals generally do not have xanthomas and, although we presume that this is an atherosclerosis susceptibility syndrome, the association with vascular disease has yet to be rigorously proven. Finally, defective chylomicron remnant clearance is also seen in E2 heterozygotes, such as those with the phenotypes E3/2 and E4/2 (37). In these individuals the milder increase in chylomicron remnants and IDL is also accompanied by a decrease in LDL cholesterol levels (38, 50–52). These people do not have xanthomas and the increase in chylomicron remnants and IDL is probably balanced out by the decrease in the LDL resulting in no increased risk for cardiovascular disease (38, 53–55).

Genetic defects in endogenous fat transport

The second lipoprotein transport pathway is the one for endogenous fats (Fig. 2). Endogenous fat transport involves the production and secretion of VLDL by the liver. VLDL are triglyceride-rich particles that also contain cholesterol. Pro-

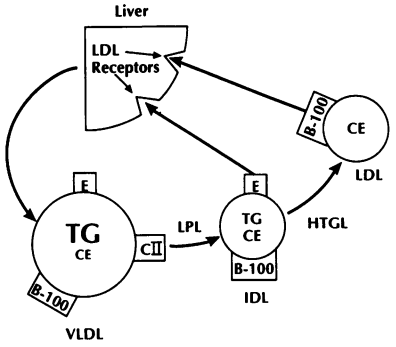

Figure 2. Endogenous fat transport pathway. Excess substrate in the liver is packaged into VLDL. After secretion, VLDL triglycerides are hydrolyzed by LPL resulting in IDL formation. IDL can either be taken up directly by liver cells through recognition of apo E by the LDL receptor, or further processed by HTGL to LDL. LDL removal is by the interaction of apo B-100 with the LDL receptor.

teins making up 10% of VLDL weight consist of the liver form of apo B, B-100; the C apolipoproteins, including apo CII; and apo E. VLDL triglycerides are hydrolyzed by LPL resulting in the formation of IDL. These can be cleared from plasma by hepatic LDL receptors that recognize and bind apo E on the IDL surface. IDL, which escape clearance, are further lipolyzed probably by HTGL, which results in the formation of LDL. LDL is a cholesterol-rich particle with apo B-100 on its surface. This form of apo B is recognized by hepatic and extrahepatic LDL receptors. Normally ~ 70% of LDL is cleared from plasma by the LDL receptor. Most of this occurs in the liver.

Genetic disorders in endogenous fat transport have also been recognized (Table II). As with chylomicrons, diminished VLDL secretion can be due to defective synthesis or secretion of apo B (12), and defects in VLDL processing to LPL or apo CII abnormalities (22–24). Problems with IDL clearance can be due to the previously described structural variation in the apo E gene (49) or to defects in the LDL receptor (10). IDL processing defects have been ascribed to deficiencies in HTGL (56, 57). Finally, LDL clearance defects can be due to abnormalities in apo B (58, 59) or in the LDL receptor (10). In the previous section on exogenous fat transport, several of these defects have been described. In this section, I will discuss in detail genetic defects in VLDL secretion and LDL clearance.

Defective VLDL secretion is seen in the disorder heterozygous hypobetalipoproteinemia (12). This disorder occurs with a frequency of ~ 1 in 1,000 in the general population (60). Affected individuals have an LDL cholesterol level of 30–50% of normal, are asymptomatic, and may even be protected from atherosclerosis. This is inherited as an autosomal dominant

Table II. Defects in Endogenous Fat Transport

	Defect	Disease
VLDL secretion	Apo B	Hypobetalipoproteinemia
		Abetalipoproteinemia
VLDL processing	LPL	LPL deficiency
	Apo CII	Apo CII deficiency
IDL clearance	Apo E	Type III hyperlipoproteinemia
	LDL receptor	Familial hypercholesterolemia
IDL processing	HTGL	HTGL deficiency
LDL clearance	Apo B	Familial defective Apo B-100
	LDL receptor	Familial hypercholesterolemia

and these individuals have one normal apo B allele and one defective allele (18, 19, 61, 62). The apo B gene contains 29 exons and 28 introns and codes for the apo B-100 polypeptide, which is 4,536 amino acids long (63). Specific apo B gene defects underlying hypobetalipoproteinemia are now being characterized. Four defective apo B alleles have been described caused by a nonsense mutation, one and four nucleotide deletions and an exon 21 deletion (19, 64, 65). All of these mutations result in premature stop codons with little to no plasma apo B derived from the defective allele.

Genetic abnormalities in endogenous fat transport due to defective LDL clearance also occur. Defects can occur in the ligand for the LDL receptor, apo B-100, or in the receptor itself. The first type of disorder is called familial defective apo B-100 (58, 59) and appears to have a frequency of ~ 1 in 500 to 1 in 1,000 in the general population, and 1 in 50 to 1 in 100 in individuals with upper decile LDL cholesterol (66). Familial defective apo B-100 is caused by a mutation in the coding sequence of the apo B gene that changes an arginine codon at amino acid 3,500 to glutamine (66). This is in the LDL receptor binding region of apo B and results in a protein with only 2–4% of normal receptor binding activity (67).

The second type of disorder is due to a defective LDL receptor and known as familial hypercholesterolemia (10). This disease has a frequency of ~ 1 in 500 in the general population and 1 in 50 in individuals with upper decile LDL cholesterol. The LDL receptor gene contains 18 exons and 17 introns (10). Many mutations in this gene have been characterized, including missense and nonsense mutations, insertions and deletions (10, 68–74). It appears that there will be dozens of LDL receptor gene mutations that underlie familial hypercholesterolemia. Thus, in genetically heterogeneous populations, it may be very difficult to achieve this diagnosis at the DNA level. On the other hand, in certain populations, founder effects have been documented that restrict the number of LDL receptor gene mutations in that population. For example, 63% of familial hypercholesterolemic French Canadian individuals have the 10-kb deletion that includes exon 1 (74). In such populations, gene diagnosis may be more useful for case finding and family counseling.

Both familial defective apo B-100 and familial hypercholesterolemia are characterized by excessive plasma LDL. Clinically, familial hypercholesterolemia is associated with a significant increase in coronary heart disease susceptibility as well as tendon xanthomas. Defective apo B has only recently been recognized and its association with coronary heart disease susceptibility must be established. Individuals with this disorder do not appear to have tendon xanthomas. Genetically, both conditions are inherited as autosomal dominants.

The three disorders heterozygous hypobetalipoproteinemia, familial defective apo B-100, and familial hypercholesterolemia all have profound effects on LDL cholesterol levels. However, their cumulative frequency is not more than 1 in 250 individuals and they obviously cannot explain the genetic variation in LDL cholesterol levels in the general population. Recently, the hypothesis was tested that other mutations involving the apo B gene exist that affect the amount of LDL cholesterol in plasma (75). This was done by taking advantage of the facts that apo B, the principal LDL protein, is not exchangeable between lipoprotein particles and that there is only one apo B per LDL particle. Therefore, plasma LDL consists of two populations, one containing apo B derived from the

maternal and the other from the paternal apo B allele. A MAb was used that recognized high- and low-affinity forms of apo B to identify individuals with allele-specific differences in the amount of apo B in their plasma. A family study confirmed that this phenotype was inherited in an autosomal dominant manner and linked to the apo B gene locus (75). A population based sample suggested that significant apo B gene mutations may exist in one in five individuals (76). This implies that the apo B gene locus may account for a significant fraction of the genetic variation in LDL cholesterol levels in the general population. The actual apo B gene lesions accounting for this observation are not yet identified.

Another genetic influence on LDL cholesterol levels is the apo E phenotype. As previously mentioned, normolipidemic E2/2 individuals have a substantial reduction in LDL cholesterol levels. In addition, the E3/2, E3/3, and E4/3 phenotypes, present in 12, 59, and 23% of Caucasians, are associated with lower, intermediate and higher levels of LDL cholesterol (50, 77–79). The findings in E3/2 individuals are due to their having half their apo E in nonfunctional form. This causes deficient liver clearance of chylomicron remnants (37) and perhaps IDL. This presumably leads to a decrease in hepatic cholesterol, upregulation of LDL receptors, and a decrease in LDL cholesterol levels. This is similar, but in a milder form, to what is seen in E2/2 individuals. The observation that E4/3 individuals have higher LDL cholesterol levels than E3/3's is surprising, since E4 and E3 function equally well in receptor binding assays. However, it is known that in the fasting state most plasma apo E resides in HDL and after fat ingestion apo E shifts from HDL to chylomicrons and their remnants (80). Recent studies have found that radiolabeled E4 is cleared from plasma faster than E3 and has less of a preference for HDL (81). In addition, E4/3 subjects clear chylomicron remnants significantly faster than E3/3's (37). This strongly suggests that E4 shifts from HDL to chylomicron remnants faster than E3. The presumed reason is that, because E4 contains no cysteine and E3 contains one residue of cysteine (the only difference), E4 in HDL cannot form disulfide bonds with other proteins (i.e., apo A-II) and is free to shift more rapidly than E3. Thus, individuals with E4 might more efficiently deliver dietary cholesterol and saturated fat to the liver with greater downregulation of LDL receptors. This could explain their higher LDL cholesterol levels. Although the common apo E genetic variation almost certainly affects LDL metabolism indirectly, it has been estimated that 8% of the variance in LDL cholesterol levels in the general population is accounted for by the three structural alleles at the apo E gene locus (82).

Genetic abnormalities in LDL metabolism can also result from the covalent attachment of a large glycoprotein called apo(a). Apo(a) is disulfide bonded to the apo B-100 moiety of LDL and the whole complex is called Lp(a) (83, 84). In contrast to LDL, this complex reacts poorly with LDL receptors (85). Lp(a) levels in the population show a skewed distribution. Many individuals have little or no Lp(a) in their plasma. However, ~ 25% have levels > 20 mg/dl. Case control epidemiologic studies show that the upper quartile of the Lp(a) distribution in the population have approximately a two- to threefold increased coronary heart disease risk (86, 87). Family studies and twin studies indicate that increased Lp(a) levels are very highly heritable (88) and cosegregate with the structural gene for apo(a) on chromosome 6 (89–92).

Recently, the gene for apo(a) has been cloned and the primary structure of the protein has been deduced (15). The gene and protein bear a striking resemblance to plasminogen. The plasminogen gene contains a signal sequence, a tail region, and kringle regions 1, 2, 3, 4, and 5, as well as a protease domain. The apo(a) gene also contains a homologous signal sequence and, although it lacks the tail and the kringle 1, 2, and 3 regions, it has many copies of the kringle 4 region, the kringle 5 region, and the protease domain. Different apo(a) alleles code for proteins with different numbers of kringle 4 repeats. Based on its range of molecular weights, apo(a) can contain between 15 and 40 kringle 4 repeats. There appears to be an inverse relationship between the amount of Lp(a) in plasma and the size of the apo(a) protein in a given individual (89–91). The mechanism for this is unknown. The apo(a) gene can be considered to have arisen from the plasminogen gene by unequal crossing over. In fact, the two genes are located very close to each other on the long arm of chromosome 6 (16, 92). Thus, apo(a) may be atherogenic by interfering with both LDL and plasminogen metabolism.

Genetic defects in reverse cholesterol transport

The third lipoprotein transport pathway is called the reverse cholesterol transport pathway (Fig. 3). This provides a means for cholesterol, which cannot be metabolized by peripheral tissues to move from these tissues back to the liver for excretion. This pathway involves HDL. Nascent HDL, which con-

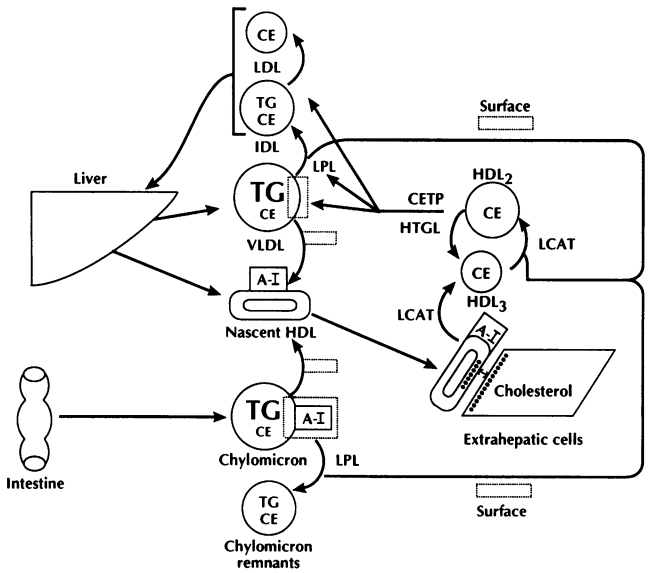

Figure 3. Reverse cholesterol transport pathway. Nascent HDL consisting of apo A-I phospholipid disks are produced by the liver. These particles attract additional surface components formed during the metabolism of triglyceride-rich lipoproteins. Nascent HDL attracts free cholesterol from tissues. This cholesterol is esterified by LCAT. This produces spherical small HDL, called HDL_3. The additional action of LCAT and LPL enlarge HDL_3 and form HDL_2, whereas the action of CETP and HTGL diminish HDL size from HDL_2 to HDL_3. The CETP mediated transport of the cholesteryl ester in HDL to apo B containing lipoproteins, VLDL, IDL, and LDL, allow uptake of this cholesteryl ester by the LDL receptor pathway in the liver and subsequent elimination of cholesterol from the body.

sists principally of apo A-I phospholipid disks, are produced primarily by the liver. These particles attract additional surface material formed during the hydrolysis of the triglyceride-rich lipoproteins, chylomicrons and VLDL, by LPL. Nascent HDL attract free cholesterol from extrahepatic cells. This cholesterol is esterified in plasma by the LCAT enzyme, which uses apo A-I as a cofactor. The cholesteryl ester produced shifts to the core of HDL changing the shape of the particle into a sphere, which we recognize in plasma as small HDL or HDL_3. The additional action of LCAT and LPL enlarge HDL_3 to HDL_2, whereas the action of CETP and HTGL tend to diminish the size of the HDL from HDL_2 to HDL_3. The CETP-mediated transport of the cholesteryl ester in HDL to the apo B-containing lipoproteins, VLDL, IDL and LDL, allow uptake of this cholesteryl ester by the LDL receptor pathway in the liver and the subsequent elimination of cholesterol from the body. This completes the reverse cholesterol transport pathway.

A few rare genetic defects in reverse cholesterol transport have been documented that lend validity to the pathway just described (6) (Table III). Defective HDL production because of an inability to synthesize apo A-I is seen in the disorder homozygous apo A-I deficiency with a frequency of < 1 in 1,000,000 in the population (6). These individuals have very low HDL levels, premature coronary heart disease, corneal clouding, and obligate heterozygotes appear to have half-normal HDL levels (93, 94). Three different mutations have been described. In type I, both apo A-I and CIII are deficient, because of a rearrangement at the apolipoprotein gene locus on chromosome 11 that inactivates these two adjacent genes (95–97). In type II, A-I, CIII, and A-IV are deficient, due to a deletion of the entire locus (98). In type III, apo A-I is deficient due to a small insertion in the apo A-I gene that alters the reading frame and causes premature termination (99).

Defective HDL metabolism due to a structural mutation in the apo A-I gene occurs in the disorder apo $A\text{-}I_{Milano}$ (100). This is an autosomal dominant disorder only described in individuals from one small Italian village. Affected individuals have 33% of normal HDL cholesterol and 60% of normal apo A-I levels, but no increased risk of coronary heart disease (100–104). The disorder is due to a mutation in the apo A-I gene changing codon 173 from arginine to cysteine (105, 106). Normal apo A-I has no cysteine and the introduction of this amino acid causes homo- and heterodimeric apo A-I containing particles. This is presumably the cause of altered HDL and apo A-I metabolism (107). Homozygous apo A-I deficiency and apo $A\text{-}I_{Milano}$ demonstrate that mutations in the apo A-I gene can have profound effects on HDL cholesterol levels. Although these particular defects are rare, it is still not certain how common other types of apo A-I defects might be in the general population. Perhaps regulatory defects or more subtle structural defects in the apo A-I gene are more common in the population and may explain some of the variation in HDL cholesterol levels between individuals.

Table III. Defects in Reverse Cholesterol Transport

	Defect	Disease
HDL production	Apo A-I	Apo A-I deficiency
HDL metabolism	Apo A-I	Apo $A\text{-}I_{Milano}$
Chylomicron and VLDL processing	LPL	LPL deficiency
	Apo CII	Apo CII deficiency
Cholesterol ester formation	LCAT	LCAT deficiency
hydrolysis	HTGL	HTGL deficiency
transfer	CETP	CETP deficiency
HDL catabolism	Intracellular processing	Tangier Disease

Defective lipoprotein processing can also cause alterations in HDL cholesterol levels. Six rare inborn errors of metabolism have been described in which this is the case (6). In the LPL and apo C-II deficiencies, the inability to process chylomicrons and VLDL causes very low HDL cholesterol levels (22–24). It is thought that this is due to the failure to transfer surface materials normally formed during triglyceride hydrolysis to HDL. In LCAT, HTGL, and CETP deficiencies, HDL level and composition are altered because of defects in cholesteryl ester formation, hydrolysis, and transfer, respectively (6, 27, 61, 62, 109, 110). Finally, in Tangier disease, low HDL cholesterol levels appear to be due to rapid HDL clearance from plasma (111). This may be due to a failure in a normal pathway of HDL uptake and retroendocytosis (112). The exact mutation affecting the intracellular processing of HDL is unknown. These inborn errors cannot explain the genetic variation in HDL cholesterol levels in the population, since their cumulative frequency is only on the order of 1 in 100,000.

In epidemiologic studies, decreased levels of HDL cholesterol are associated with increased susceptibility to coronary heart disease, whereas high levels are associated with resistance (113). The reason for this is uncertain. It is possible that low HDL cholesterol levels could represent an inefficient functioning of the reverse cholesterol transport pathway and be atherogenic in this manner. Alternatively, low HDL cholesterol levels could reflect other aspects of lipoprotein transport, such as less efficient lipolysis of triglyceride-rich lipoproteins, and this in turn may cause susceptibility. In either case, the common genetic explanations for low and high HDL cholesterol levels in the population that affect atherosclerosis susceptibility are not known.

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