Lipid Disorders and Mutations in the APOB Gene

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Background: Plasma lipoproteins are important determinants of atherosclerosis. Apolipoprotein (apo) B is a large, amphipathic glycoprotein that plays a central role in human lipoprotein metabolism. Two forms of apoB are produced from the APOB gene by a unique posttranscriptional editing process: apoB-48, which is required for chylomicron production in the small intestine, and apoB-100, required for VLDL production in the liver. In addition to being the essential structural component of VLDL, apoB-100 is the ligand for LDL-receptor-mediated endocytosis of LDL particles.

Content: The study of monogenic dyslipidemias has revealed important aspects of metabolic pathways. In this review, we discuss the regulation of apoB metabolism and examine how APOB gene defects can lead to both hypo- and hypercholesterolemia. The key clinical, metabolic, and genetic features of familial hypobetalipoproteinemia and familial ligand-defective apoB-100 are described.

Summary: Missense mutations in the LDL-receptor-binding domain of apoB cause familial ligand-defective apoB-100, characterized by increased hypercholesterolemia and premature coronary artery disease. Other mutations in APOB can cause familial hypobetalipoproteinemia, characterized by hypercholesterolemia and resistance to atherosclerosis. These naturally occurring mutations reveal key domains in apoB and demonstrate how monogenic dyslipidemias can provide insight into biologically important mechanisms.

Lipoproteins are spherical complexes of lipids and apoproteins that stabilize the lipid emulsions and also act as ligands for receptor-mediated processes. Lipoprotein metabolism involves a complex network of biochemical processes and pathways, including their assembly, secretion, transport, processing, and clearance. Apolipoprotein B (apoB), a large amphipathic glycoprotein, plays a central role in human lipoprotein metabolism. The human apoB gene (APOB) is located on chromosome 2, and the same gene produces two forms of apoB in circulating lipoproteins, apoB-48 and apoB-100. ApoB species are named according to a centile scale. ApoB-48 is identical to the amino-terminal 48% of apoB-100 and is produced by the small intestine, whereas full-length apoB-100 is produced in the liver. A unique mRNA editing process enables the APOB gene to make the two structurally related but discrete isoforms that have different functions.

ApoB-48 is required for chylomicron production, and apoB-100 is an essential structural component of VLDL and its metabolic products, intermediate-density lipoprotein (IDL) and LDL. In addition to its structural role, apoB-100 is a ligand for LDL-receptor-mediated endocytosis of LDL. Essentially all circulating apoB is associated with lipoproteins, and unlike most other apoproteins, apoB cannot exchange freely among lipoprotein particles. Increased plasma concentrations of apoB-containing lipoproteins have been demonstrated to be key risk factors for the development of atherosclerosis.

Historically, the study of monogenic conditions, including those of plasma lipoprotein abnormalities, has been an effective means to reveal and provide insight into key biologically relevant metabolic mechanisms. The study of naturally occurring mutations in affected families has been useful in identifying important domains of apoB governing the metabolism of apoB-containing lipoproteins. This review will focus on the importance of apoB in the regulation of plasma LDL-cholesterol concent-

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Nonstandard abbreviations: apo, apolipoprotein; IDL, intermediate-density lipoprotein; MTP, microsomal triglyceride transfer protein; ER, endoplasmic reticulum; FHBL, familial hypobetalipoproteinemia; FDB, familial ligand-defective apoB-100; ABL, abetalipoproteinemia; CAD, coronary artery disease; and FH, familial hypercholesterolemia.
trations and the role of mutations in APOB that can give rise to either hypo- or hypercholesterolemia.

**Structure of the APOB Gene/APOB mRNA Editing**

In adult humans, apoB-100 is produced in the liver (4536 amino acids; 100%) and apoB-48 in the intestine (2152 amino acids; 48%) via a unique mRNA editing process (1). The 43-kb APOB gene is located on the short arm of human chromosome 2. It consists of 29 exons, of which exon 26, at 7572 bp, is the largest exon and encodes more than one half of the full-length protein. A novel posttranscriptional editing process occurring on the 14.5-kb mRNA leads to apoB-48 production. In brief, a RNA-specific cytidine deaminase, apoB mRNA editing enzyme catalytic complex 1 (apobec-1), binds to and acts on the cytosine molecule at base 6666 of the mRNA to create a uracil, which leads to the glutamine 2153 (CAA) codon being converted to a termination (UAA) codon (2). Apobec-1 is produced only in intestinal epithelial cells in adult humans. It is the editing process that determines the apoB isoform to be synthesized, which in turn dictates the type of lipoprotein, either chylomicron or VLDL particle, to be assembled.

**apoB Protein Structure**

Because of its large size, propensity to form insoluble aggregates in aqueous solutions, and its sensitivity to proteolytic degradation, the primary structure of apoB was not elucidated until 1986 (3). ApoB includes a polymorphic signal peptide of either 24 or 27 amino acids that is cotranslationally cleaved to produce a mature protein of either full length (100%; 4536 amino acids; 550 kDa) apoB-100 or apoB-48 (48%; 2152 amino acids; 265 kDa). The predicted molecular mass of apoB-100 is 513 kDa, and the higher apparent molecular mass of the protein found in the circulation is the result of glycosylation at 16 sites in apoB (4).

ApoB contains hydrophobic lipid-binding regions as well as hydrophilic regions that interact with the aqueous plasma environment. These appear to be arranged as a series of amphipathic α-helices and β-sheet domains, designated NH$_2$β$_{α_1}$β$_{α_2}$β$_2$-α$_2$-β$_α$-COOH (Fig. 1) (5). ApoB-48 comprises the first two domains. The β$_α$1-domain consists of the first 1000 amino acids of apoB and is a globular domain with homology to lipovitellin, an egg yolk lipoprotein (6). It is this domain with which microsomal triglyceride transfer protein (MTP) binds during apoB assembly. The β$_{α_1}$- and β$_α_2$-domains are irreversibly associated with the lipid core of the lipoprotein, whereas the α-helices of the α$_{α_1}$- and α$_{α_2}$-domains, which are similar to those found in the “exchangeable” apoproteins, are thought to exhibit reversible lipid binding.

ApoB contains a LDL-receptor-binding domain that is involved in the uptake of LDL as well as VLDL and IDL from the plasma. The LDL-receptor-binding domain has been localized to the carboxyl-terminal portion of apoB, specifically, residues 3359–3369 (site B) (7). Site B is highly conserved among species and is very similar to the receptor-binding region in apoE. Normal binding of LDL to the LDL receptor was shown in transgenic mice expressing apoB in which site B was replaced with the equivalent apoE receptor-binding domain (7). Conformational changes involving interaction between amino acid residues Arg-3500 and Trp-4369 have been demonstrated to be important to induce the structure of apoB-100 necessary for binding to the LDL receptor (8).

The mature protein contains 25 cysteine residues, 16 of which are involved in intramolecular disulfide linkage. Of the eight disulfide bonds, seven occur within the first 1000 residues of apoB (the β$_α$1-domain) and are important for the proper folding of the amino-terminal end of apoB and essential for apoB-containing lipoprotein assembly and secretion (9). Cys-4326 forms a disulfide bond with apo(a), which covalently links apoB and apo(a) to form lipoprotein(a) (10). The atherogenicity of apoB-containing LDLs is linked to their affinity for artery wall proteoglycans. Residues 3359–3369, in addition to binding the LDL receptor, were identified as the major proteoglycan-binding sequence in apoB-100 (11). Although this region is not present in apoB-48, apoB-48-containing lipoproteins have been implicated in atherogenesis. Another region, residues 84–94, was identified as a proteoglycan-binding domain in apoB-48, and there is evidence to suggest that this region in apoB-100 is “masked” by the carboxy terminus and hence unavailable to bind vessel wall proteoglycans (12).

**Regulation of ApoB Synthesis**

Assembly of VLDL in the hepatocyte requires the coordinated synthesis of apoB-100 and lipids. ApoB is synthesized in the rough endoplasmic reticulum (ER) and moves to the lumen of the ER while being translated through targeting by the signal peptide, which is then cleaved. The association with lipid may occur during apoB translation and its translocation across the ER. Proper folding of the amino terminus is partly mediated through the formation of disulfide bonds, which is required to initiate lipid transfer. Transfer of lipids to nascent apoB occurs during apoB translation and its translocation across the ER, a process facilitated by MTP.

The sequence elements within apoB required for lipid recruitment have not been precisely defined, but it is clear that apoB length, hydrophobic sequences, and an adequate supply of lipid are important factors in VLDL.
assembly and secretion. The amount of apoB-100 secreted by the hepatocyte is a balance between the amount synthesized and the amount degraded within the cell before secretion. There is accumulating evidence that apoB production is regulated posttranslationally at the steps of protein translocation across the ER membrane into the lumen and intracellular degradation.

TRANSCRIPTIONAL AND TRANSLATIONAL MODULATION
Transcription of \( APOB \) is regulated by a promoter \((-150\) to \(+124\)) in combination with either the liver-specific regulatory region \((-899\) to \(-5262\) plus an enhancer in intron 2) or the intestinal enhancer (a 315-bp sequence that lies 56 kb upstream) \((13)\). The observation that apoB mRNA concentrations remain relatively stable in the presence of numerous factors known to influence apoB secretion suggests posttranslational regulation. ApoB is constitutively synthesized in excess of its requirement for lipid transport, the excess being degraded within the cell. The variations in the relative abundance of apoB mRNA reported in vitro tend to be small.

TRANSLLOCATION, PARTICLE ASSEMBLY, AND DEGRADATION
Most secretory proteins are synthesized in the ER and are rapidly translocated to the lumen. In contrast, most nascent apoB that fails to assemble properly into lipoprotein on the luminal side of the ER becomes membrane bound and is inefficiently or partially translocated. A two-step model of lipoprotein assembly has been widely accepted and is inefficiently or partially translocated. A two-step model of lipoprotein assembly has been widely accepted as the mechanism for apoB-containing lipoprotein production \((14)\). In this model, a lipid-poor apoB is produced, followed by addition of bulk neutral lipids to the core (Fig. 2).

The hydrophobic nature of apoB means that correct folding and stability require the addition of lipids cotranslationally. A “lipid pocket” model, formed by interaction of the amino-terminal 1000 residues of apoB with MTP, has been proposed as the mechanism of the initial lipidation of apoB \((15)\). The 97-kDa MTP and 55-kDa protein disulfide isomerase form a heterodimer that acts as a chaperone as well as facilitating lipid transfer from the ER membrane to nascent apoB \((16)\).

Formation of mature VLDL is thought to occur through fusion of two precursors: the partially lipidated apoB and a preformed triglyceride-rich droplet the size of VLDL \((14)\). Lipid droplet formation in the smooth ER is MTP-dependent, whereas fusion of the two precursors to form mature VLDL occurs independently of MTP \((14)\).

ApoB secretion is regulated through the intracellular degradation of apoB. Approximately one half of newly synthesized apoB is degraded rather than secreted. There are two mechanisms by which nascent apoB can be degraded. The first mechanism, the ubiquitin-proteasome pathway, occurs when the initial lipidation of apoB by MTP fails because of insufficient lipid. The apoB then becomes covalently modified by conjugation to ubiquitin and targeted for degradation by proteasomes \((17)\). Proteasomal degradation of apoB is ubiquitin-dependent in the ER and ubiquitin-independent in the Golgi \((18)\). The second pathway involves the LDL receptor, which can also target and prevent secretion of presecretory apoB as well as reuptake of nascent apoB-containing particles \((19)\).

Lipid availability regulates apoB production; inadequate lipid leads to incorrect folding of the protein and degradation. The size of the VLDL particle synthesized is also determined by the availability of lipid; excess triglyceride synthesis leads to the production of large, triglyceride-rich VLDL \((14)\). However, debate continues over which neutral lipid—cholesterol, cholesteryl ester, or triglyceride—is most important in the regulation process.

Lipid Disorders and Mutations in the \( APOB \) Gene
Assembly of VLDL in the hepatocyte requires the coordinated synthesis of apoB-100 and lipids. The ability of apoB-100 to interact with the LDL receptor depends on both sequence and conformation and is fundamental for the regulation of plasma cholesterol in humans. Two genetic disorders of lipid metabolism attributed to mutations in the \( APOB \) gene are familial hypobetalipoproteinemia (FHBL; OMIM 107730) and familial ligand-defective apoB-100 (FDB; OMIM 107730)

Mutations in the \( APOB \) gene causing the production of a truncated molecule can cause FHBL and hypcholesterolemia, whereas defects in the carboxy terminus of the LDL-receptor-binding domain of apoB cause FDB, a form of hypercholesterolemia. These naturally occurring mutations reveal key domains in apoB and demonstrate how monogenic dyslipidemias can provide insight into biologically important mechanisms.
Hypobetalipoproteinemia

Many factors, such as a strict vegan diet, illness, and high-dose statin therapy, can cause hypobetalipoproteinemia. The more common secondary causes in the hospital setting include cachexia, malabsorption, malnutrition, severe liver disease, and hyperthyroidism. Primary causes include abetalipoproteinemia (ABL; OMIM 200100), chylomicron retention disease (OMIM 246700), and FHBL (20).

FHBL

FHBL is a rare autosomal codominant disorder of lipoprotein metabolism characterized by low plasma concentrations of total cholesterol, LDL-cholesterol, and apoB (20). Many nonsense, frameshift, and splicing mutations in the APOB gene leading to formation of prematurely truncated apoB forms have been reported in individuals with FHBL. There is some evidence that molecular changes other than truncations of APOB lead to FHBL.

Biochemical and Clinical Findings

Heterozygotes for FHBL are often asymptomatic but have plasma LDL-cholesterol and apoB concentrations that are one fourth to one third of normal (below the 5th percentiles for age and sex). The clinical and biochemical features of FHBL in homozygotes and compound heterozygotes are very similar to those of ABL (21). Diagnosis can be made according to inheritance pattern; obligate heterozygotes for ABL have LDL-cholesterol concentrations within reference values for healthy individuals. ABL, a very rare autosomal recessive disorder, is caused by mutations in the MTP gene and is characterized by the virtual absence of apoB-containing lipoproteins in the plasma (22). Clinical features of ABL and homozygous FHBL can include acanthocytosis, deficiencies in fat-soluble vitamins secondary to malabsorption, atypical retinitis pigmentosa, and neuromuscular abnormalities (21). Acanthocytosis, a cell membrane defect of erythrocytes, has also been observed in FHBL heterozygotes (20). Retinitis pigmentosa and other neuropathies are primarily a result of deficiencies in fat-soluble vitamins, especially vitamin E, attributable to their impaired transport.

Molecular Diagnosis

Approximately 50 different mutations in APOB have been described that interfere with the translation of full-length apoB (20, 23). These mutations in apoB cause the production of truncated apoB isoforms of various lengths because of the missing carboxyl-terminal portion of the molecule. These truncations are named according to a centile system and range from apoB-6.46 to apoB-89 (21). Most mutations are nucleotide substitutions and deletions in exon 26 (Fig. 3). Other mutations are shorter truncations and splice-site mutations. The frequency of FHBL attributable to truncated forms of apoB has been estimated at 1 in 3000 (24). Shorter truncations, such as apoB-31, tend to be found in more dense and lipid-poor HDL fractions. Truncated apoB species shorter than this are not detectable in plasma.

We described the first case of APOB-linked hypobetalipoproteinemia that is caused by a missense mutation, R463W (25). Heterozygotes for R463W had the typical phenotype with plasma apoB concentrations less than one half of normal, whereas homozygotes had barely detectable apoB. The mechanism responsible for the impaired secretion of VLDL appears to involve impaired ER exit and enhanced binding to MTP (25). Furthermore, we have identified another missense mutation, L343V, associated with FHBL (26). An apparent sporadic case of FHBL caused by a “de novo” mutation of apoB was recently described (27).

Some cases of FHBL are not linked to APOB. A susceptibility region for FHBL has also been identified at 3p21.1–2 (28). In addition, some individuals heterozygous for MTP mutations (i.e., ABL “carriers”) have LDL-cholesterol and apoB concentrations similar to those seen in FHBL heterozygotes (29).

Lipid and Lipoprotein Metabolism

The possible reasons for the lower-than-expected concentrations of apoB include decreased hepatic secretion of the apoB-containing lipoproteins or the up-regulation of LDL receptors, leading to enhanced clearance rates for VLDL and LDL particles produced by the wild-type allele (30). Nonsense-mediated decay, a process by which mRNA species containing nonsense mutations are targeted for degradation, could also play a role (31).

Because of low concentrations of LDL-cholesterol in FHBL individuals, FHBL may represent a longevity syndrome. Recently, considerable attention has been focused on the importance of triglyceride-rich lipoproteins as a cardiovascular disease risk factor. FHBL individuals typically have low triglyceride concentrations; however, whether apoB gene defects that lead to FHBL modulate triglyceride-rich lipoprotein metabolism is unclear and may depend on specific mutations (30).

Total plasma concentrations of truncated apoB species generally do not exceed 0.05–0.1 g/L and are commonly <0.03 g/L. This is <10% of the amount expected from a wild-type apoB-100 allele. Truncated apoB species larger than apoB-29 are detectable in plasma, this appearing to be the minimum length of apoB that is required for
MTP-dependent lipoprotein assembly. Those apoB species that are not detected in plasma appear to be unable to acquire sufficient lipid, leading to intracellular degradation rather than secretion (32).

Stable isotope tracer methodology has been used to study the in vivo kinetics of apoB in FHBL individuals. It was shown that truncated forms of apoB are produced at lower rates than apoB-100 (33). In addition, clearance of truncated species, especially apoB-75 and apoB-89, which contain the LDL-receptor-binding domain, is faster than truncated species, especially apoB-75 and apoB-89, which contain the LDL-receptor-binding domain, is faster than the clearance of apoB-100 (34, 35). On the basis of the “ribbon and bow” model of apoB structure on LDL particles, the absence of the carboxy terminus of apoB-100 would lead to enhanced receptor binding (8). The secretion rate was found to be linked to the degree of truncation of the apoB species, such that secretion was reduced by 1.4% for each 1% of apoB truncated (33).

TREATMENT
Treatment in homozygotes includes restriction of dietary fats to prevent steatorrhea and long-term vitamin E and A supplementation to prevent progression of the neuromuscular and retinal degenerative disease (20, 36). Vitamin E supplementation in FHBL heterozygotes with low vitamin E concentrations has also been recommended to prevent neurologic defects.

LIVER DYSFUNCTION AND STEATOSIS
Fatty liver has been reported in FHBL individuals; impaired VLDL assembly could lead to accumulation of lipids in hepatocytes. Recently, magnetic resonance spectroscopy has been used as a tool to assess liver fat in FHBL individuals with a range of apoB truncations (apoB-4 to apoB-89) (37). FHBL heterozygotes were observed to have a liver fat content threefold higher than control individuals (37).

MURINE MODELS
Genetically engineered mice bearing a variety of different truncated apoB isoforms have helped elucidate the pathophysiology of FHBL. A mouse model for FHBL, producing apoB-38.9, has been generated (38). These mice exhibit a 75% reduction in apoB-100 and have reduced triglyceride secretion from the liver. Apob1/1 mice have secretion rate for newly synthesized triglyceride that is decreased by 40%, and in apoB1/1 mice, the rate is decreased by 70% (38). The lower-than-expected concentrations of apoB-100 were recently shown to be a result of decreased secretion rather than decreased synthesis (39). In apoB-38.9-heterozygous primary hepatocytes, synthesis of apoB-100 was reduced to the expected 50% of controls, whereas secretion rates were reduced by 80%.

IN VITRO STUDIES
The assembly and secretion of apoB-containing lipoproteins have been studied by use of a variety of cell lines as well as primary hepatocytes. In vitro studies using truncated apoB constructs have been instrumental in investigating apoB assembly and secretion. Experiments in COS cells showed that the minimum requirement for MTP-dependent buoyant lipoprotein production is the initial 884 amino acids (apoB-19.5) (40). ApoB isoforms larger than this underwent efficient conversion to buoyant lipoproteins when coexpressed with MTP. Although truncation variants shorter than this, such as apoB-17, can be secreted, they do not require MTP and produce a lipid-poor form of apoB. A recent study showed that the region between the carboxy terminus of apoB-37 and apoB-42 determined the secretion efficiency and intracellular stability of the protein (41).

FDB
Defects in the LDL-receptor-binding domain of apoB can cause autosomal dominant hypercholesterolemia. FDB is a disorder of LDL metabolism characterized by hypercholesterolemia and premature atherosclerosis (42). Several mutations in the APOB gene affecting the binding affinity for the LDL receptor have been identified.

BIOCHEMICAL AND CLINICAL FINDINGS
FDB is characterized by increased plasma LDL-cholesterol and apoB concentrations with triglyceride concentrations within the reference interval, by tendon xanthomas, and by premature coronary artery disease (CAD). FDB cannot be clinically distinguished from heterozygous familial hypercholesterolemia (FH; OMIM 144010), but the hypercholesterolemia in FDB is less severe, the presence of tendon xanthomas less common; there also appears to be a lower incidence of CAD in FDB. Furthermore, it is important to note that plasma LDL-cholesterol concentrations are below the 95th percentile of the population in more than 25% of FDB heterozygotes. FDB homozygotes have plasma LDL-cholesterol concentrations more comparable to those of heterozygous rather than homozygous FH.

MOLECULAR DIAGNOSIS
As stated above, FDB cannot readily be clinically distinguished from FH. Several mutations in the LDL-receptor-binding domain of apoB have been described that are associated with hypercholesterolemia with an autosomal codominant inheritance pattern. The most common, R3500Q, affects ~1 in 500 individuals of European descent and involves the substitution of a glutamine for arginine at position 3500 (43, 44). Genotyping for the R3500Q mutation is available at many specialist biochemical genetics laboratories, but an independent missense mutation at the same position, where a tryptophan is substituted for arginine (R3500W), has also been described and is prevalent in hyperlipidemic patients of Chinese or Malay descent (45). R3531C impairs LDL-receptor binding to 49% of normal and increases LDL-cholesterol, but not to the extent of R3500Q (46). The R3480W substitution also leads to defective LDL-receptor
binding (8). All four mutations have been unequivocally linked to defective LDL-receptor binding and hypercholesterolemia, are located within a stretch of 51 amino acids, and lead to the loss of an arginine residue. More recently, a new variant, H3543Y, was identified by denaturing gradient gel electrophoresis in a German study group (47). This mutation had a prevalence of 0.47% compared with 0.12% for the R3500Q mutation in patients undergoing diagnostic coronary angiography for suspected CAD (47). It is likely that more FDB-causing mutations will be found.

LIPI D AND LIPO PROTEIN METABOLISM
The mutations appear to alter the three-dimensional structure of the binding area so that LDL particles with the mutated apoB have reduced binding affinity for the LDL receptor, leading to the accumulation of particles containing the mutant apoB (7). Stable-isotope studies in R3500Q heterozygotes showed a decreased production rate and fractional catabolic rate of LDL- apoB (48). An increase in clearance of LDL precursors, mediated by apoE, as well as a decrease in conversion of IDL to LDL could explain the milder phenotype in FDB compared with FH.

TREATMENT
Although diet is the first line of treatment of hypercholesterolemia, it generally fails to achieve target LDL-cholesterol concentrations (<2.6 mmol/L) when used alone in FDB. Because the principal abnormality in FDB is an increase in plasma LDL-cholesterol, drugs that target this lipoprotein are indicated. Hydroxymethylglutaryl-CoA reductase inhibitors or statins are the mainstay of pharmacotherapy, but other options include bile-acid-binding resins, niacin, and the cholesterol absorption inhibitor ezetimibe. Combination drug treatment may be necessary. Surprisingly, FDB heterozygotes and homozygotes respond to the LDL-cholesterol-lowering effects of statins, presumably because normal LDL receptors are present and VLDL-remnant clearance is enhanced. Statin therapy is of use in delaying or preventing the onset of CAD, but effective primary prevention requires early diagnosis by “cascade” lipid screening of relatives of known FDB individuals.

IN VITRO STUDIES
A mechanism explaining the defective receptor binding of LDL seen in FDB has been suggested from a series of in vitro studies. A ribbon and bow model of apoB on LDL suggests that mutations at codons 3500 and 3531 cause conformational changes in apoB, thereby making the binding site less accessible (7). The carboxyl-terminal bow-region of apoB-100 functions as a negative modulator of receptor binding and inhibits binding of VLDL to the LDL receptor. There is evidence for a direct interaction between Arg-3500 and Trp-4369 that maintains the correct conformational structure of apoB-100 in LDL (8). Furthermore, this observation can explain how the carboxy terminus of apoB-100 interacts with the backbone of apoB-100 that enwraps the LDL particle.

Conclusion
The study of monogenic conditions, including those of plasma lipoprotein abnormalities, has been an effective means to reveal and to provide insight into key biologically relevant metabolic mechanisms. Defects in the APOB gene can cause either hypocholesterolemia or hypercholesterolemia, depending on the mutation. The study of naturally occurring mutations in affected families has been useful in identifying important domains of apoB governing the metabolism of apoB-containing lipoproteins. Diagnosis at the molecular level has a bearing on treatment and is becoming a part of the routine diagnostic repertoire.

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