The 1985 Nobel Prize in Physiology for Medicine was awarded to two physicians from Southwestern Medical Center in Dallas, Texas. Michael Brown, MD, and Joseph Goldstein, MD, received this honor “for their discoveries concerning the regulation of cholesterol metabolism.”

They postulated that regulatory abnormalities of 3-hydroxy 3-methylglutaryl coenzyme A reductase were the cause of familial hypercholesterolemia (FH). This disorder had been known for many years, given the known clustering of tendon xanthomas (TX), vascular atheromas and premature onset of coronary artery disease. Many other individuals including Frederickson and Levy in the 1960’s advanced the concept that FH involves the apoprotein and cholesterol components of LDL. Goldstein and Brown discovered the hepatic cell surface LDL receptor (LDLR) and later demonstrated that FH was due to mutations in gene coding.

FH is a co-dominantly inherited disorder of lipid metabolism characterized by a defective allele (or alleles) in the gene coding for LDLR. It is highly penetrant and has a gene dosage effect (i.e., homozygotes are affected to a greater extent than heterozygotes). This results in dysfunction or structural abnormalities of the LDLR which reduce the catabolism of LDL particles and increase LDL plasma concentration.

The LDLR gene resides on the short arm of chromosome 19 and is comprised of 18 exons, spanning 45 kb. The gene codes for an 839 amino acid single chain glycoprotein which binds LDL particles and allows their delivery to the lysosomes for degradation.

Five classes of mutations have been identified, ranging from null alleles which fail to produce the protein, to defects which uniquely block multiple steps in the process of transport, binding and recycling. When LDLR is abnormal, the removal rate of LDL-C declines, and the plasma level increases. Excess LDL is deposited in scavenger cells and forms TX and atheromas. There are more than 1,600 mutations of LDLR known to cause FH.

The prevalence of FH is well-defined: it is one of the most common genetic disorders. Heterozygotes number about 1:500 persons in the general population, increasing to 1:50 when a founder effect is present, such as in French Canadian, Finnish, Christian Lebanese and South African populations.

The disease provides a model system for other treatable genetic disorders, especially given the clinical consequences of premature myocardial infarction. Of concern is that an estimated 80% of FH in Western countries remains undetected, in spite of advancing knowledge of the disease. This is undoubtedly influenced by the substantial variability in the phenotypes associated with FH.

Mean LDL-C concentration at all ages in heterozygotes is 2-3x that of normal subjects. That number is doubled or tripled in homozygotes. Minor structural alterations in some particles result in a decreased triglyceride (TG) content, and an increase in the cholesterol:phospholipid ratio.
ratio. However, when LDL from an FH homozygote is injected into a normal subject, the LDL is normally metabolized, suggesting that the structural variances are not clinically significant. HDL-C levels in FH patients are slightly lower than in normals, and TG levels are also lower or similar depending on environmental factors.2

FH has traditionally been diagnosed when elevated plasma TC and LDL-C is combined with family or individual history of premature heart disease. Two sets of criteria logically are used in screening for this disease given a known bimodal probability distribution of LDL-C: one for the general population and one for subjects in whom a 1st or 2nd degree relative is known. Using LDL-C alone as a criterion therefore is prone to underdiagnosis.10,14,15

The “gold standard” for unequivocal diagnosis is DNA testing for genetically identified mutations, although the Dutch Lipid Clinic Network requires one additional clinical criterion. There is relatively weak concordance between phenotype and genotype. Testing for the genetic defect is a complex, expensive process with limited availability. Careful choice of appropriate candidates is advisable.2,11

A widely used genetic diagnostic platform in Europe and the U.S., includes a microarray for the detection of common point mutations and small deletions in LDLR and apolipoprotein B (ApoB) genes. If this is negative, then full LDLR coding sequence analysis is done to diagnose large rearrangements by quantitative fluorescence based multiplex polymerase chain reaction analysis. The presence of new disease causing mutations is ascertained by sequencing the promoter region of the 18 exons and flanking intronic regions of the LDLR.18

### Worldwide, there are three diagnostic tools for FH:15

1) Simon Broome Register Group (SBRG) in the UK
   a. Results are classified as “definite” or “possible”:
      i. TC(LDL) >290(>190) in the index patient or 1st/2nd degree relative + TX is considered definite FH
      ii. Above criteria + family history myocardial infarction or TC>290 is considered possible FH

2) Make Early Diagnosis Prevent Early Death (MEDPED) in the U.S.
   a. Utilizes age-related cutoffs for TC (LDL) which are further delineated by whether results pertain to general population or to patient with 1st, 2nd or 3rd relative with FH
      i. <20 yrs age TC(LDL) 270 (200)mg/dL; 20-29 yrs 290 (220); 30-39 yrs 340 (240); >40 yrs 360 (260)
      ii. Lowered strata in the setting of positive family history

3) Dutch Lipid Clinic Network (DLCN)
   a. Definite, probable, or possible categories
   b. Score derived from family history of LDL>95th percentile; family history premature vascular disease; 1st degree relative with TX or arcus cornealis (AC); LDL >95th percentile in child <18 yrs age; TX or AC present at <45 yrs; elevated LDL-C; positive DNA testing for LDLR
   c. >8 points is definite; 6-8 points probable; 3-5 points possible

The clinical utility of DNA testing has been validated in many Western populations. Generally speaking, approximately 55% of patients over 14 years of age with a clinical suspicion of FH evaluated with genetic testing were found to have functional mutations in LDLR or ApoB gene loci.19

Among those patients the presence of TX either in the proband, or a 1st or 2nd degree relative was strongly correlated with identification of a genetic abnormality. This appears to be the most significant predictor of molecular defect when coupled with LDL-C >190 mg/dL. Mutation positive patients were more often female with higher levels of TC and LDL, and lower TG.

HDL and high levels of Lp(a) appear to be less predictive of identifiable mutations. In the 45% of patients in whom mutations were not identified, the prevalence of type 2 diabetes mellitus and body mass index was higher.

Using a set of criteria which included LDL>190 mg/dL (with family history, or >220 mg/dL without), combined with TX created a significant correlation (p < 0.0001) with the presence of molecular defects. With these criteria, 9/10 subjects with LDLR or ApoB mutations will be detected. Using the same criteria, when TX were either absent or unknown, the frequency of the FH mutation carrier decreased to 46%, but retained acceptable statistical sensitivity and specificity.12,19

Conclusions can be drawn from the above discussion.

1) TX are highly specific for FH in the setting of elevated TC and/or premature coronary artery disease in the family. They should be carefully looked for on physical examination, including the use of tools such as x-ray or ultrasound of the Achilles tendon.

2) MEDPED has emerged as the most
utilitarian diagnostic tool with its simplicity and good accuracy. When patients or family members do not have TX, the use of age adjusted LDL cutoffs is very important diagnostically.

3) Utilizing the approach outlined maximizes the likelihood of genetic confirmation of molecular defects. This can be used to facilitate genetic counsel, and cascade screening. The detection of a mutation also reinforces adherence to diet and drug therapy.

Phenotypically, FH is also known to be caused by mutations in ApoB, gain of function mutations involving paraprotein convertase subtilin/kexin 9 (PCSK9) and several other rare inherited disorders. Study of PCSK9 also represents promising therapeutic opportunities.5,6,20

Familial defective ApoB 100 (FDB) and classic FH are often clinically indistinguishable. ApoB is a non-exchangeable lipoprotein, containing over 4,500 amino acids, which is required for the synthesis of TG-rich lipoproteins in the liver (VLDL) and intestine (chylomicrons). All atherogenic lipoproteins contain ApoB as key architectural component.21

The ApoB gene is located on chromosome 2 and contains 29 exons and 28 introns. ApoB is the ligand required for clearance of LDL-C by the LDLR. It was identified during study of patients with normal LDLR function, who exhibited delayed clearance of LDL.

FDB (aka FLDB—familial ligand defective ApoB), also inherited in an autosomal dominant fashion, is characterized by elevated TC and LDL-C, premature heart disease and frequently with TX. At least four mutations are known, the most prevalent of which is an arginine/glutamine substitution resulting from a missense mutation at the 3500 codon. Often the levels of LDL-C are not as high as in heterozygous FH, and this is one feature which reduces the utility of the MEDPED criteria for diagnosis. In these patients the remnant lipoproteins which depend on ApoE rather than ApoB are still cleared appropriately, or even to a greater extent than in normals which may account for the lower level of LDL-C.22,23

FH has traditionally been diagnosed when elevated plasma TC and LDL-C is combined with family or individual history of premature heart disease.

Finally, the FH phenotype formerly known as Autosomal Dominant FH3 was mapped in France in 1999. Kindred have since been identified in Utah, Sardinia, and Spain. This gene is located on the short arm of chromosome 1 and codes for PCSK9. Several mutations have been discovered. Patients are often clinically indistinguishable from FH although typically LDL is lower, and there is greater responsiveness to statin therapy.

PCSK9 activity correlates with LDLR activity, possibly in a modulatory fashion, and promotes LDLR degradation. Hence, inhibition of PCSK9 increases the clearance of LDL particles, because the LDLR density and activity is enhanced and potentiates statin activity.2,3

Phenotypic variation in FH may also be modulated by ApoE polymorphisms, and variable alleles of this apoprotein (E2,E3, orE4) may have different penetrance in FH subjects versus normal.24,25 Gene-gene and gene-environment interactions play a prominent role in phenotypic expression of the disease.

Clinicians are also often called upon to differentiate between FH and familial combined hyperlipidemia. Clinical tips are easily accessible in the literature to assist with this challenge.14,16

This review is intended to enhance awareness of the physiologic mechanisms which characterize this clinically important genetic disease, to elucidate the diagnostic criteria, and identify guidelines which will help determine the need for genetic testing to confirm the clinical suspicion of FH. ■

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References listed on page 31.