When faced with a new patient whose low-density lipoprotein (LDL) cholesterol level is 239 mg/dL, who has no other diseases, and who takes no drugs affecting lipid metabolism, a doctor is likely to make the diagnosis of Familial Hypercholesterolemia (FH) on the spot. If the patient confirms that she has had this problem since she was a young girl and that her father and older brother are affected as well, this will close the case. However, even if she objects that her cholesterol was normal when she was in college and swears this will close the case. However, even if she objects that her cholesterol was normal when she was in college and swears that her parents have no lipid problems, our confidence in the diagnosis will not falter, and we would just assume that per-
cholesterol was normal when she was in college and swears this will close the case. However, even if she objects that her cholesterol was normal when she was in college and swears that her parents have no lipid problems, our confidence in the diagnosis will not falter, and we would just assume that personal and family history may not be accurately recalled. We all know that the criteria for the diagnosis of FH are more complex, but xanthomas and arcus senilis are rarely present, and thickening of the Achilles tendons is hard to confirm by manual examination, coronary artery disease is often delayed in subjects without other risk factors, and evaluation of family history in most cases is based on patient report, not on direct investigation. This leaves us with 1 piece of information, the LDL cholesterol level, which we know can be moderately increased by many factors and raises above the 95th percentile (or about 190 mg/dL in adults) only for severe clearance problems. In the absence of renal, hepatic, autoimmune, or thyroid diseases, if the patients are not taking medications that notoriously can raise LDL cholesterol levels, an LDL clearance problem is attributable to a faulty interaction between the LDL receptor (LDLR) and its ligand on the LDL particle (apoB). Classically, FH was defined as a dominantly inherited disease caused by mutations in the LDLR gene. It was later determined that a dysfunctional mutation in apoB also causes an FH phenotype. More recently, the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9), as a regulator of LDLR levels on hepatic plasma membranes, has introduced another player capable of producing, via dominant inheritance of gain-of-function mutations, the FH phenotype. Because the term FH should apply only to the disease caused by an LDLR mutation, a new definition has been coined, Autosomal Dominant Hypercholesterolemia (ADH), to encompass FH and the diseases caused by apoB and PCSK9 mutations.

The article from Ahmad et al, published in the current issue of Circulation: Cardiovascular Genetics, tells us that this simplistic assumption is plainly wrong. Out of 91 unrelated subjects with a classic presentation of ADH, they found 30 carriers of LDLR mutations and 1 carrier of the dysfunctional apoB 3500 mutations, whereas 60 subjects had no culprit mutation in any of these genes, and thus their ADH was unexplained. This unexpected negative outcome occurred in 27 of the 35 African American patients, 15 of the 29 whites, 10 of the 18 Hispanics, and 8 of the remaining 9 patients defined as other (but including mostly individuals of Asian origin). It must be said that the investigation of the 3 candidate genes was not so thorough as to rigorously and definitively exclude a role for each gene in each case of unexplained ADH, as the approach included the sequencing of the flanking regions and all 18 exons of LDLR (followed by Multiplex Ligation-dependent Probe Amplification analysis to detect larger rearrangements such as exon deletions or duplications), and that of exon 26 of apoB, and exons 2, 4, and 7 of PCSK9 (in both cases including all the known disease-causing mutations). However, this approach is standard and even more comprehensive than that used in similar studies published previously, and it is not likely that many more cases would be identified by fully sequencing the 3 genes and by extending the search to promoter regions and some extra length on both sides, because the prevalence of regulatory mutations was about 0.3% in a large Spanish cohort of FH subjects. Is it then possible that the entry criteria allowed for the inclusion of non-ADH forms of genetic dyslipidemia, such as FCHL and ARH?
This possibility was not investigated, because the authors only excluded the very rare type III hyperlipidemia (which does not raise LDL) by use of apoE genotyping. Their argument against FCHL is that TG levels were similar between those with and those without ADH, but that does not mean much, because the reported distribution of TG levels went up to 498 mg/dL and that of HDL cholesterol went down to 26 mg/dL. Without a more detailed presentation of the data, it is not difficult to envision the possibility of several cases of familial combined hyperlipidemia (elevated TG, elevated LDL, low HDL) in the unexplained ADH group countered by a few cases of secondary hypertriglyceridemia in the ADH group to balance the TG averages between groups. This is not unlikely given the very wide distribution of body mass index among these patients, with the highest value well within the range of morbid obesity, suggesting that insulin resistance was likely present to affect TG metabolism. A study of Italian children showed that the diagnostic accuracy of LDLR sequencing to identify true FH subjects was about 50% when the inclusion criteria were rigorously based on exclusive and severe LDL elevations, but dropped significantly (to <10%) when also including children with an FCHL phenotype or with milder LDL elevations. With regard to ARH, this condition has a phenotype similar to ADH, but the mutation is in a protein, LDL receptor adaptor protein, that needs complete loss of function to cause the disease and is therefore transmitted as a recessive disorder. In theory, it seems simple to discern between a recessive and a dominant hypercholesterolemia. In practice, this depends on access to and accurate evaluation of the proband’s parents (including paternity testing), as it is not enough to know that a parent has high cholesterol or is taking a statin to make the case for a dominantly inherited trait. Ahmad et al reports that if first-degree relatives were not available, diagnosis was inferred by history recall. This leaves open the possibility of a recessive transmission. However, this argument is mostly academic, because the prevalence of ARH is extremely low, and it is unlikely to be the cause of even 1 case among any 91 unrelated subjects with extreme hypercholesterolemia. These results are compatible with the possibility that ADH is also caused by a novel undiscovered gene. Another possibility is epigenetic changes in 1 of the culprit loci, inherited but not demonstrable through DNA sequencing.

Evidence had been published before for a so-called diagnostic gap between phenotypic definition and molecular characterization of ADH, with as many as 25% of well-characterized ADH subjects not showing mutations in any of the 3 loci when investigated with the most comprehensive technical protocols. The fact that in ADH children the diagnostic accuracy of molecular studies is closer to 95% could be interpreted to suggest that either nongenetic factors responsible for FH phenocopies may develop more commonly later in life or information about family history is more reliable when the proband is a child rather than an adult. Even in children, although the capture rate for genetic mutations is low when the diagnostic criteria are more inclusive, only 50% of probable FH subjects were confirmed as carriers of LDLR mutations when the LDL cutoff was the 95th percentile (≥150 mg/dL). Because all previous reports were done in relatively homogenous populations or in groups where specific mutations are amplified by a founder effect, it was to be expected that results would be even more puzzling when obtained from a variety of racially diverse ADH subjects representing the much more typical patient mix seen in an established referral center of a large U.S. metropolitan area. Even considering that, the results of this article are drastic and should shake our confidence in diagnosing the easiest to detect and most exemplary of inherited metabolic diseases. The solution to this problem should be the stringency of the LDL inclusion criteria. Although the vast majority of ADH subjects will cluster above the 95th percentile of the LDL cholesterol distribution, the vast majority of dwellers of the top 5th percentile will not have ADH. It is interesting to note that clinical differences between ADH and unexplained cases in this study included a 50-point higher mean LDL cholesterol among mutation carriers (around 290 mg/dL versus 240 mg/dL in noncarriers). An LDL of ≥290 mg/dL in adults (≥220 mg/dL in children) with at least 1 affected first-degree relative was classically reported as the mean value of true FH heterozygotes and found to be 98% specific and 87% sensitive for the diagnosis of FH. Thus, it seems apparent that to close the diagnostic gap for ADH, we need to raise the bar of LDL inclusion way up from the current recommendations, which in most cases requires evidence of an untreated LDL >190 mg/dL.

The question remains, however, of what may cause extreme elevations in LDL cholesterol when the 3 culprit genes or other genes are not involved. Ahmad et al studied plasma PCSK9 levels and found no differences between ADH and unexplained cases. This finding does not exclude the possibility of nongenetic modifications of PCSK9 via posttranscriptional structural changes or partnering with other plasma or tissue proteins, which may enhance its receptor-binding and degradation function or its sequestration and retention in specific tissues such as the liver. It is worth noting that PCSK9 may be genetically modified to increase its LDLR-degradation efficiency 25 times without changes in its plasma levels, and, more relevantly to this argument, PCSK9 is likely to have a paracrine and autocrine effect, with its local concentration in the perihepatocellular environment being the strongest determinant of function. Proteins such as annexin-2 and resistin are known to interact with PCSK9 and possibly modify its function or redirect its trafficking and tissue sequestration. Of particular importance, resistin levels are increased in obesity, and resistin-PCSK9 interactions can be a cause of hypercholesterolemia among these patients. The patients in the study by Ahmad et al were on average obese (mean body mass index >30), and several likely were morbidly obese. Investigation of resistin levels or resistin-PCSK9 complexes among these patients could provide a better diagnostic lead. In unique circumstances, an FH phenotype can be acquired later in life in the course of an autoimmune disease as a consequence of a blocking antibody against the LDLR. A patient of this kind, described many years ago, had a clinical presentation mimicking FH (minus the inheritance) and succumbed to a heart attack at a young age. However, it is unlikely that monoclonal antibodies would explain any of the cases in this cohort.

The last point of discussion is on the importance of making a genetic diagnosis when caring for a patient with severe
hypercholesterolemia. One can expect that the good doctors who performed this study sat down with each patient to discuss the results of the genetic tests and provided 2 different bottom lines depending on whether the diagnosis of ADH was confirmed. For the 31 subjects with a disease-causing mutation, the message must have been, more or less, “we confirm that your disease is caused by a genetic mutation,” whereas the other 60 subjects will have been told, “we could not find a specific reason for your high cholesterol, but it is still a very dangerous condition.”

We need to remember that the direct and proximal cause of early cardiovascular disease is the extreme hypercholesterolemia phenotype and not mutations in any gene. Studies show that a genetic diagnosis, unless linked to obvious therapeutic improvements, does not make a difference in a patient’s perception of quality of care. Moreover, the inability to confirm a diagnosis at the molecular level may exclude a patient in dire need from therapies that are inappropriate reserved for orphan diseases with canonical genetic substrates, failing to include phenocopies of equal severity and exclude a patient in dire need from therapies that are inappropriate reserved for orphan diseases with canonical genetic substrates, failing to include phenocopies of equal severity and may cause a catastrophe.

The phenotype is the problem, however acquired.

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**References**


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When It Looks Like Familial Hypercholesterolemia…but Is Not
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