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GENETIC DIAGNOSIS OF FH: WHAT IS NEW AND WHAT IS OPTIMAL?

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Abstract

Familial hypercholesterolemia (FH) is a common hereditary lipid disorder inherited as an autosomal co-dominant condition in that heterozygotes are not as severely affected as homozygotes. Affected patients have high lifetime LDL levels leading to premature vascular disease and especially coronary artery disease (CAD). Genetic defects are found mainly in the LDL receptor gene (*LDLR* 90%), Apo-Lipoprotein B gene (*APOB* 5−10%) and the proprotein convertase subtilisin kexin type 9 (*PCSK9* 1−2%). Rare mutations have also been found in other genes including *APOE*, *STAP1* and *LDLRAP1*. Treatment for high LDL using lipid-lowering drugs is effective, and has been shown to reduce the risk of premature CAD and early mortality in the condition. It could be emphasized that early diagnosis of FH is essential for an efficient patient management plan and the WHO, NICE and the European Atherosclerosis Society all recommend that molecular testing is the best approach for early detection of FH especially using cascade testing of families. It is important to use a combination of clinical scoring criteria in concert with molecular mutation screening to establish a diagnosis of FH.

Conventional genetic testing of FH has been DNA sequence analysis by Sanger sequencing and capillary electrophoresis, and MLPA for detection of larger deletions/duplications. Recently, NGS technologies have become more cost-efficient for smaller laboratories, and have now been adopted by many diagnostic laboratories. This allows for increased numbers of patients to be tested, and the potential investigation of larger numbers of genes involved in each disease, albeit with the increased analysis and interpretation which accompanies that. Although this detection level was lower than might be expected using accepted clinical criteria, it demonstrated that primary-care screening via NGS analysis of a limited number of target genes could be a viable approach to patient-finding.

Keywords

Genetics, Familial Hypercholesterolemia, Next-generation Sequencing