EDITORIAL

Genetic Screening of Familial Hypercholesterolaemia.

Cardiovascular pathologies, such as myocardial infarction, cerebrovascular accidents, and peripheral vascular ischemia, are commonly observed in individuals with elevated levels of cholesterol, triglycerides, and low-density lipoprotein (LDL) levels, as these factors are atherogenic. Beyond diet and lifestyle, genetic defects involving lipoprotein synthesis, transportation, and lipid metabolism also contribute to elevated lipid levels. Familial hypercholesterolemia (FH) is one such genetic disorder, inherited in an autosomal dominant manner, leading to the elevation of low-density lipoprotein cholesterol (LDL-C). FH has a global prevalence of 0.32%, affecting approximately 1 in 313 individuals [1]. A recent study by Chua et al., [2] reported a higher prevalence of FH in Malaysia with 1 in 100 individuals affected by FH [2]. Using the Dutch Lipid Clinic Network Score (DLCNS) to screen 5,130 participants, Chua et al., identified 55 potential FH cases, although they reported a low detection rate of less than 1% [2]. Improved detection rates could be achieved with mass parallel molecular identification for mutations in apolipoprotein genes, complemented by family cascade screening. Screening within families where the molecular defect is known is relatively straightforward; however, the numerous mutations associated with FH complicate the genetic analysis, leaving most patients with FH to remain undiagnosed and miss out on potentially life-saving treatments.

The LDL receptor (LDLR) gene is the most common mutation in FH, accounting for approximately 90% of cases, and it plays a key role in the cellular uptake of LDL-C. The next common mutation seen in apolipoprotein B (ApoB), accounts for 5-10% of cases, while proprotein convertase subtilisin / kexin-type 9 (PCSK9) mutations occur in fewer than 3% of cases [3].

In Malaysia, genotyping of clinical FH patients was carried out by Lye S-H et al, [3] and Razman AZ et al, [4]. Lye S-H et al. used a high throughput microarray platform, identifying significant risk-associated single nucleotide polymorphisms (SNPs) in 76.60% of patients. Similarly, Razman AZ et al, used next-generation sequencing (NGS), and identified 41 pathogenic variants across LDLR, ApoB, PCSK9, and LDLRAP1 genes in clinical FH subjects. They concluded that genetically confirmed FH prevalence was approximately 1:427, with a detection rate of 0.2% [4].

Implications of Genetic Screening in FH:

Chua et al. estimated that there are about 320,000 individuals with FH in Malaysia. In a primary care or physician's clinic setting, applying the DLCNS screening tool may be time-intensive. However, creating referral pathways for patients with high lipid levels, obesity, diabetes, or a family history of premature coronary events could help streamline the DLCNS process. Those classified as definite, probable, or possible FH could then undergo molecular testing for FH-related genes.

Identifying pathogenic variants in FH remains challenging, especially given the wide range of genes analysed in parallel through NGS. The distinction between mutations (permanent nucleotide changes) and polymorphisms (variants with >1% frequency) often leads to confusion regarding pathogenicity. To address this, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommend using “variant” with specific classifications: pathogenic, likely pathogenic, uncertain

significance, likely benign, or benign. Determining variant pathogenicity, especially for newly identified variants, remains complex.

Genetic screening aims to identify individuals with pathogenic variants for timely intervention, typically through the administration of statins or, in the case of PCSK9 mutations, PCSK9 inhibitors. Screening young individuals (under age 45) with acute coronary syndrome could be especially beneficial, as they may gain substantial advantages from the interventions. These include cholesterol-lowering medications, natural supplements, dietary cholesterol reduction, and lifestyle modifications for overall cardiovascular health.

Keywords: *Familial hypercholesterolemia, genetic screening, next-generation sequencing.*

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