Genetics of Early Onset Familial and Non-familial Coronary Artery Disease in a Cohort of Egyptian Patients

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Background:
Ischemic heart disease (IHD) is the main cause of death worldwide. Many factors are known to increase the risk of IHD. Dyslipidemia is one of the treatable risk factors that have polygenic and monogenic inheritance patterns. Familial hypercholesterolemia (FH) is the most common monogenic disorder affecting 1:100-250. It is estimated to affect up to 5% of patients with premature IHD. Dutch Lipid Clinic Network (DLCN), Simon Broom and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria are made to establish the clinical diagnosis of FH, nevertheless, less than 10% of the cases with premature IHD are diagnosed as FH prior to presenting as IHD. Autosomal dominant (AD) FH is caused by mutations in some known genes. The most common causative gene is **LDLR**, and less commonly by **APOB, PCSK9** and **APOE** genes. Autosomal recessive (AR) FH is caused by mutations in **LDLRAP1**, in addition to **ABCG5/8** genes that cause sitosterolemia, which mimics FH. Genetic diagnosis is thus essential: to confirm the patient's diagnosis, choose the optimum lipid-lowering treatment and provide cascade screening for the family members of affected patients.

Aim and objectives:
To apply next-generation sequencing technology (NGS) to detect pathogenic variants in **LDLR, APOB, PCSK9, APOE, LDLRAP1** and **ABCG5/8** genes in premature CAD patients who are at high risk of having monogenic FH.

Methods:
The study involved 48 patients with premature IHD who were clinically diagnosed with at least possible FH according to DLCN criteria and were recruited from the Cardiology department, Alexandria Faculty of Medicine. Patients with secondary causes of dyslipidemia or above 40 years with a negative family history have been excluded. All patients who gave informed consent to participate in the study were offered genetic counseling, full clinical history was taken including detailed family history and construction of at least 3 generation pedigree, clinical examination and measuring lipid profile. Baseline LDL-C was calculated for patients on lipid-lowering treatment according to the type and doses. NGS was performed for all patients using the TruSight Cardio Sequencing kit which contains 174 genes causing monogenic cardiac diseases including the 7 FH genes of interest. Variant analysis and interpretation were done according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Result:

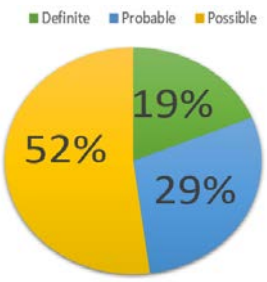

Figure (1): Classification of patients according to DLCN criteria

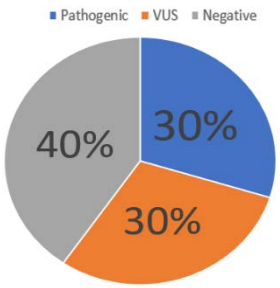

Figure (2): Genetic testing results.
VUS: variants of uncertain significance

Conclusion:
FH is a modifiable risk factor for IHD that should be suspected in any patient with premature IHD and a positive family history. In Egypt, the high prevalence of consanguinity contributes to a significant incidence of both homozygous AD and AR FH. Genetic diagnosis should be offered to all patients with definite or probable FH, as it not only confirms the diagnosis of FH but can also enhance the management of their LDL-C levels and facilitate cascade screening for their family members.

Keywords:
IHD, CAD, Familial hypercholesterolemia, genetic, Egyptian.

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