PRIMEVIEW

FAMILIAL HYPERCHOLESTEROLAEMIA

nature REVIEWS DISEASE PRIMERS

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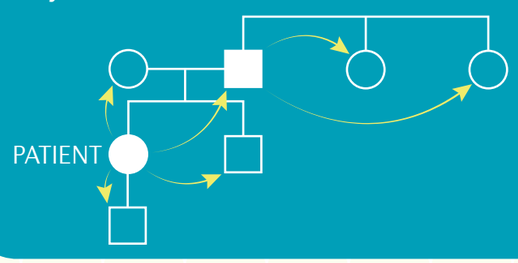
Familial hypercholesterolaemia is an inherited disorder caused by mutations in genes encoding proteins that are involved in the metabolism of low-density lipoprotein (LDL) cholesterol. Individuals with familial hypercholesterolaemia have chronically elevated plasma levels of LDL cholesterol, which can lead to premature cardiovascular disease (CVD).

DIAGNOSIS

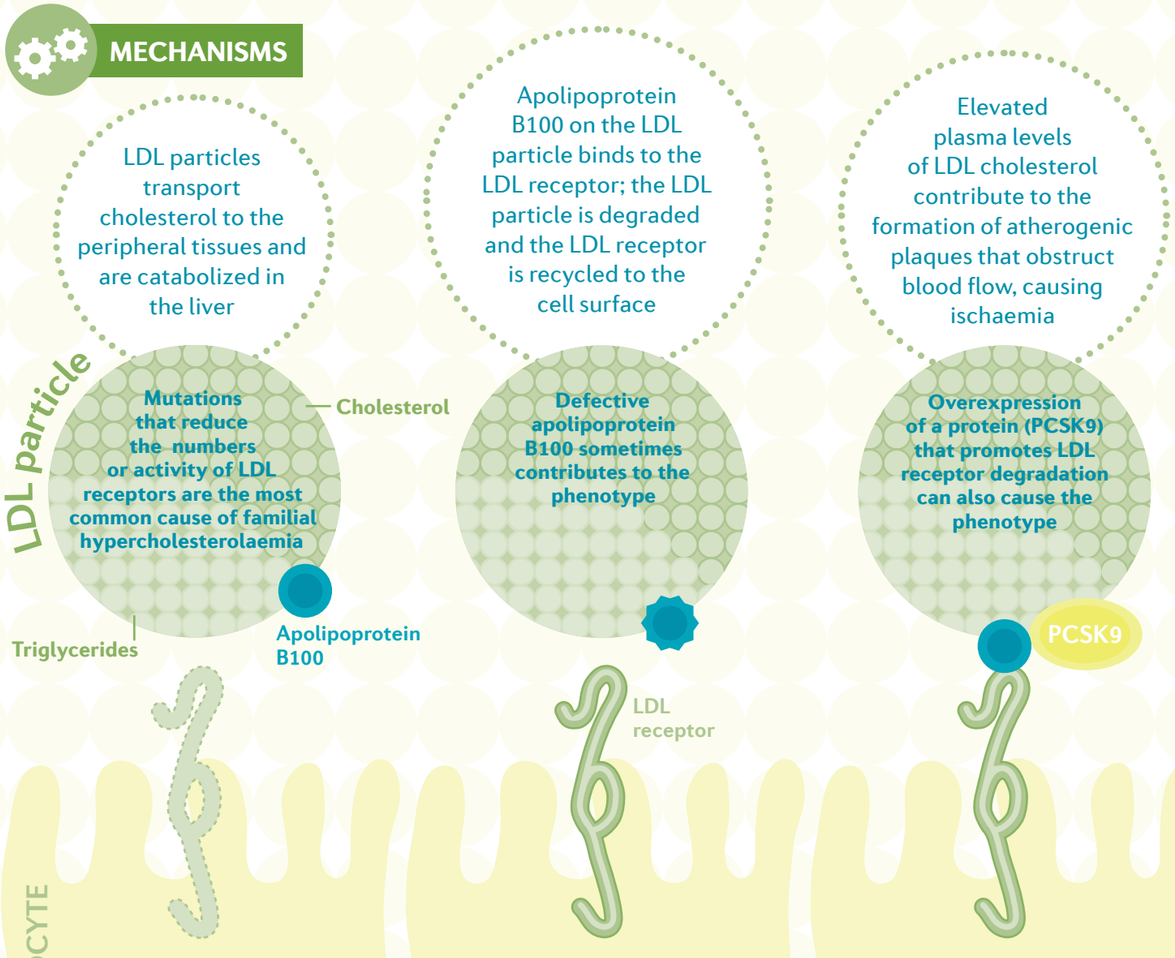
Hypercholesterolaemia is mostly asymptomatic; lipid deposits within tendons (xanthomas) or around the eyes (xanthelasmata) can form, but not in all patients. Thus, many individuals are diagnosed only in early adulthood, when plasma lipid profiles are analysed after the patients have experienced a premature CVD episode. Clinical diagnosis is generally based on LDL cholesterol levels and a family history of hypercholesterolaemia or CVD. The identification of a causative genetic mutation can confirm the clinical diagnosis but is not essential, as therapeutic decisions are guided by the degree of LDL cholesterol increase.

SCREENING

Early diagnosis and treatment of familial hypercholesterolaemia are crucial to reduce the risk of CVD. Cascade genetic screening can identify family members of a patient who also carry the same causative mutation.



MECHANISMS



EPIDEMIOLOGY

The prevalence of familial hypercholesterolaemia is estimated at ~1 in 250–300 individuals, although data vary in different populations and according to the diagnostic criteria used. Individuals with familial hypercholesterolaemia have an increased risk of early CVD, especially myocardial infarction and stroke. Additional risk factors for CVD include advanced age, elevated body mass index, type 2 diabetes mellitus, hypertension and lifestyle habits, such as unhealthy diet and smoking.

MANAGEMENT

The goal of management is the prevention of atherosclerotic CVD through lipid-lowering therapy, which includes lifestyle interventions and pharmacotherapy. Statins (which inhibit cholesterol synthesis) are the first-line treatment, but often additional drugs (such as ezetimibe, which reduces cholesterol absorption, and inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), which reduce LDL receptor degradation) are required to achieve the treatment targets: >50% reduction in the initial LDL cholesterol levels (in primary prevention of CVD) or specific LDL cholesterol levels (in secondary prevention).

OUTLOOK

The application of next-generation sequencing-based diagnostic methods will probably result in the identification of additional genetic variants that can modulate the clinical phenotype. New LDL cholesterol-lowering approaches, in particular PCSK9 inhibition via gene silencing, are under development. The use of cascade screening should be encouraged, as the cost-effectiveness is similar to that of other widely implemented screening programmes (for example, for breast cancer). Finally, the immediate challenge is to maximize awareness of familial hypercholesterolaemia among health care providers and patients to promote early diagnosis and treatment.

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