Familial hypercholesterolaemia: taking advantage of a founder effect for early diagnosis and treatment

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Short Title: Familial hypercholesterolaemia

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Abstract

Objective: To characterise the mutations in the LDL receptor gene in patients with heterozygous familial hypercholesterolaemia (FH) living in Northwestern Greece and to determine, if any, the geographical distribution of these mutations.

Methods: DNA analysis for the LDL receptor gene was performed (using restriction enzyme method or direct sequencing) in unrelated patients attending our lipid clinic with a clinical diagnosis of heterozygous FH.

Results: The 1775G>A LDL receptor gene mutation is the most common mutation causing familial hypercholesterolaemia in our area and is restricted in a mountainous area called Tzoumerka, which shows a founder effect.

Conclusion: The screening of the population in Tzoumerka area is strongly recommended for the detection of new FH patients. Furthermore, patients originating from Tzoumerka and attending other lipid clinics with a clinical diagnosis for FH could have their DNA tested for the above mutation.
Familial hypercholesterolaemia (FH) is a most common genetic disorder characterised by increased serum total and low-density lipoprotein (LDL) cholesterol levels, tendon xanthomata and premature coronary artery disease. The frequency of heterozygosity is 1:500, whereas the frequency of homozygosity is 1:1,000,000 in most populations. The clinical syndrome is caused by mutations in the LDL receptor gene. We have recently reported seven LDL receptor gene mutations causing FH in northwestern Greece as well as their geographic distribution (1). The most common LDL receptor gene mutation (1775G>A–Sicily/Foggi/Naples4–amino acid change G571E), located in exon 12, accounted for 33% of the FH patients and was identified in 29 patients (22 heterozygotes and 7 homozygotes). This mutation has been previously detected in Italy, German, Poland, Austria and Belgium (Database of LDLR gene mutations in FH: http://www.ucl.ac.uk/fh) but for the first time in Greece [1]. The 1775G>A mutation is restricted in a mountainous area called Tzoumerka (population of about 3000 people) near the city of Ioannina in northwestern Greece. Until recently, the complete geographical isolation of the above area and the high degree of close breeding/inbreeding in the population may explain the relatively higher frequency of FH, thus, strongly suggesting a founder effect. Interestingly, this mutation is a class V mutation, which means that the LDL receptor retains the ability to bind and internalise its ligand but fails to release it in the endosome and thus the receptor does not recycle to the cell surface [2]. It has been pointed out that individuals with these mutations do have lower lipid levels, less severe coronary artery disease and are more responsive to hypolipidemic drug therapy compared to patients carrying other types of LDL receptor gene mutations [2]. In fact, total and LDL cholesterol levels of our homozygous patients with this mutation are relatively low (440±80mg/dl and 354±78mg/dl, respectively) and are comparable to those of heterozygotes with other
types of mutations. In addition, our homozygous patients showed significant decreases in the LDL cholesterol levels after treatment with high doses of statins (mean change of LDL cholesterol by 24.9%) [3]. Accordingly, the clinical follow-up and screening of the population in the Tzoumerka area is strongly recommended for the prevention of premature heart disease through the early detection and treatment of FH. After thorough medical examination of FH index patients, information on the health status of their relatives could be obtained through personal or telephone interviews. In addition, names and addresses of all living siblings and parents, irrespective of loss of regular contact, will provide invaluable information for the construction of family pedigrees (In pedigrees: circles denote female individuals; squares, males; blackened symbols, affected individuals; single lines, matings or sibling relationships; double lines, consanguinity matings). In a close community, such as Tzoumerka community, the possibility of consanguinity between the parents, may be determined by tracing the ancestors of each proband. Similarly, first and second degree relatives of each identified FH proband may be traced down, through the family pedigree. In the small community of Tzoumerka, the FH patients are likely to be aware of the health status of their relatives, irrespectively, of whether they live in Tzoumerka or if they have emigrated elsewhere in the world. Therefore, the relatives of the probands may be contacted in order to identify family members who are at higher risk for developing cardiovascular complications due to the presence of LDL receptor gene mutations. Detailed family history data have been proposed to be effective in identifying high-risk families for targeted intervention [4]. For the Tzoumerka area, the early clinical diagnosis of FH patients and the verification of the disease at the DNA level, through community genetics, ultimately provides a valuable tool for the prevention of premature heart disease in this area. Furthermore, these
approaches may lead to the identification of new homozygous FH patients, since their lipid profile mimics that of heterozygous FH patients carrying other types of LDL receptor gene mutations, and if so genetic counselling could be given to them.

References:


