Novel low density lipoprotein receptor variant linked to early onset acute myocardial infarction in a patient with familial hypercholesterolaemia

Fatima A Bangash, Carl RH Antbring and David S Wald
Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6 BQ, UK
Corresponding author: David S Wald. Email: d.s.wald@qmul.ac.uk

Lesson
A novel LDL-receptor gene variant was found responsible for previously undetected familial hypercholesterolaemia and acute myocardial infarction in a young man.

Keywords
familial hypercholesterolaemia, low-density lipoprotein receptor, myocardial infarction, cholesterol

Introduction
Familial hypercholesterolaemia (FH) is the most important and commonly inherited cause of premature coronary heart disease. It is an autosomal dominant disorder affecting about two in every 1000 individuals resulting in elevated low-density lipoprotein (LDL)-cholesterol levels from birth. Half of untreated males and 20% of the untreated females diagnosed with FH suffer a coronary heart disease event by age 50. Treatment to lower LDL-cholesterol, using statins, is effective in prevention.

A diagnosis of FH can be made clinically (by history, clinical examination and measuring serum cholesterol levels) or by DNA analysis and identifying a mutation in one of three genes that regulate blood cholesterol levels (PCSK9, APOB and LDLR). More than 1700 mutations have been identified and almost all are within the LDLR gene. The advantage of DNA analysis is that it provides a confirmatory test in patients with a raised LDL cholesterol, in whom the cholesterol may be elevated for other reasons (such as high dietary saturated fat intake), and provides an accurate and simple method for cascade testing of first degree relatives of an affected individual (half of whom will be affected), so that preventive treatment can be started before the onset of disease. DNA analysis alone, however, is imperfect, because not all mutations are known and genetic variants have been identified in people without elevated LDL cholesterol levels or a history of coronary heart disease, leading to uncertainty in the management of such patients and their families. This case report provides an important correlation between a novel mutation and its clinical phenotype.

Case history
A 26-year-old man of Indian and Kenyan descent presented to a London cardiac centre with a two-hour history of central chest pain that had started abruptly and was associated with palpitations. He had no history of cardiac disease but had smoked 20 to 30 cigarettes a day for the past 11 years. There was no history of preceding recreational drug use expected to cause coronary heart disease. His family history (Figure 1) was notable for early onset coronary heart disease (below the age of 60 years) in second-degree relatives (two maternal uncles and maternal grandparents and one paternal uncle).

A resting 12-lead electrocardiogram showed ST elevation in leads II, III and AVF, consistent with inferior wall myocardial infarction and he was taken directly to the cardiac catheter laboratory for emergency angiography. The angiogram showed an occluded right coronary artery (Figure 2(a)), which was treated by emergency thrombectomy (clot removal) and insertion of a single intracoronary stent (Figure 2(b)). His chest pain and ST elevation resolved once flow down the right coronary artery was restored. No other significant coronary artery narrowings were identified in the left anterior descending coronary artery or left circumflex coronary artery.

Blood tests revealed an elevated level of cardiac troponin (0.5 ng/mL), a raised total cholesterol level (non-fasting) of 7.5 mmol/L and LDL of 4.6 mmol/L. This indicated a clinical diagnosis of possible FH on the basis of Simon Broome diagnostic criteria; total cholesterol ≥7.5 mmol/L and family history of myocardial infarction <60 years of age in a second-degree relative. A genetic diagnosis was later confirmed.
using direct Sanger sequence analysis of the promoter and 18 exons of the LDL-receptor (LDLR) gene, Apolipoprotein B (APOB) exon 26 and Proprotein convertase subtilisin/kexin type 9 (PCSK9) exon 7. Multiplex Ligation-dependent Probe Amplification (MLPA) was also carried out to detect the presence of large deletions or duplications in the LDLR gene (Gene reference sequence – LDLR: NM_000527.3, APOB: NM_000384.2, PCSK9: NM_174936.2). The patient was found to be heterozygous for the c.2289G>T transition in exon 15 of LDLR gene (Figure 3). This change is predicted to result in substitution of glutamic acid for aspartic acid at amino acid residue 763 (p.Glu763Asp).

Following the acute myocardial infarction, the patient was started on five new daily cardiac medications; ramipril 10 mg, bisoprolol 7.5 mg, aspirin 75 mg, clopidogrel 75 mg and atorvastatin 80 mg. He was discharged from hospital after two days and reviewed in clinic after 12 weeks. His total cholesterol had reduced from 7.5 mmol/L to 2.7 mmol/L. He had stopped smoking and had returned to his normal level of physical activity. Cascade testing has been offered to his parents.

Discussion

The mutation identified in this patient (c.2289G>T) has been reported once before, as a new variant of uncertain pathogenicity. The case history we present here shows that this mutation is pathogenic, associated with both high total and LDL cholesterol and a clear clinical coronary heart disease event in the third decade of life.
The *LDLR* c.2289G>T substitution is on exon 15. This exon encodes an *LDLR* domain that serves as an attachment site for *O*-linked sugar chains. O-glycosylation is essential for LDL function and in its absence the *LDLR* is degraded and surface expression of the receptor is reduced. Since the *LDLR* is involved in transporting LDL into the cells, reduced *LDLR* surface expression would be expected to reduce the uptake of LDL into the cells and increase serum cholesterol levels, as observed here. The link between *LDLR* dysfunction and increased atherosclerotic events has also been shown.

c.2289G>T was one of four novel variants of uncertain pathogenicity described by Hooper et al. and is one of a total of 1741 mutations in the *LDLR* gene described to date. Uncertainty over the disease-causing potential of new mutations arises when they are discovered, often during family screening, in people with no history of coronary heart disease or raised serum cholesterol. The clear presentation with acute myocardial infarction and raised

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**Figure 3.** Localisation of the heterozygous mutation c.2289G>T, (p.Glu763Asp) in Exon 15 of *LDLR* gene. GenBank Accession Number of the wild-type *LDLR* gene sequence is NM_000527.3. (a) Wild-type *LDLR* gene sequence and (b) affected patient’s *LDLR* gene variant sequence.
serum cholesterol in the patient presented here helps resolve this uncertainty for c.2289G>T, an observation that is helpful in guiding the clinical management of this patient, his relatives and other patients who may be identified in the future with the same \textit{LDLR} mutation.

\textbf{Declarations}

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