Whole-exome sequencing in an extended family with myocardial infarction unmask familial hypercholesterolemia.

Familial hypercholesterolemia (FH) is an autosomal-dominant disease leading to markedly elevated low-density lipoprotein (LDL) cholesterol levels and increased risk for premature myocardial infarction (MI). Mutation carriers display variable LDL cholesterol levels, which may obscure the diagnosis. We examined by whole-exome sequencing a family in which multiple myocardial infarctions occurred at a young age with unclear etiology. Whole-exome sequencing of three affected family members, validation of the identified variant with Sanger-sequencing, and subsequent co-segregation analysis in the family. The index patient (LDL cholesterol 188 mg/dL) was referred for molecular-genetic investigations. He had coronary artery bypass graft (CABG) at the age of 59 years; 12 out of 15 1st, 2nd and 3rd degree relatives were affected with coronary artery disease (CAD) and/or premature myocardial infarction (MI). We sequenced the whole-exome of the patient and two cousins with premature MI. After filtering, we were left with a potentially disease causing variant in the LDL receptor (LDLR) gene, which we validated by Sanger-sequencing (nucleotide
substitution in the acceptor splice-site of exon 10, c.1359-1G> A). Sequencing of all family members available for genetic analysis revealed co-segregation of the variant with CAD (LOD 3.0) and increased LDLc (>190 mg/dL), following correction for statin treatment (LOD 4.3). Interestingly, mutation carriers presented with highly variable corrected (183-354 mg/dL) and on-treatment LDL levels (116-274 mg/dL) such that the diagnosis of FH in this family was made only after the molecular-genetic analysis. Even in families with unusual clustering of CAD FH remains to be underdiagnosed, which underscores the need for implementation of systematic screening programs. Whole-exome sequencing may facilitate identification of disease-causing variants in families with unclear etiology of MI and enable preventive treatment of mutation carriers in a more timely fashion.