# Homozygous familial hypercholesterolemia due to *APOB* genetic variant with unusual clinical course

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A 29-year-old patient was admitted to our center with suspected familial hypercholesterolemia (FH). The patient had no comorbidities, nor was she taking any medications. Her lipid profile was: total cholesterol 248 mg/dl, low-density lipoprotein cholesterol (LDL-C) 191 mg/dl, high-density lipoprotein cholesterol (HDL-C) 44 mg/dl, and triglycerides 64 mg/dl. Physical examination showed no relevant abnormalities. Mean carotid intima-media thickness was 0.37 mm and 0.49 mm in the left and right internal carotid arteries and coronary calcium score was 2. The patient scored 4 on the Dutch Lipid Clinic Network scale which is a diagnostic tool for FH. Next-generation sequencing revealed a homozygous variant in the apolipoprotein B (*APOB*) gene (c.10580G>A p.[Arg3527Gln]). Moreover the heterozygous APOE rare variant, denoted as c.460C>T p. (Arg154 Cys), was present in the patient. In the course of the cascade screening, we acquired data concerning the proband's family (Figure 1). Detailed analysis of family history revealed that the parents of the proband were 2nd line cousins. Dietary consultation and rosuvastatin 20 mg daily with ezetimibe 10 mg daily were prescribed with LDL-C reduction to 62 mg/dl by 67%.

According to WOBASZ II (*Wieloośrodkowe Badanie Stanu Zdrowia Ludności*, Multi-center National Population Health Examination Survey), lipid disorders and unsatisfactory treatment efficacy remain a major problem in the Polish population [1]. Inherited lipid abnormalities referred to as FH is genetically heterogeneous and the most common are variants within LDL receptor (*LDLR*), *APOB*, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes. Hypercholesterolemia

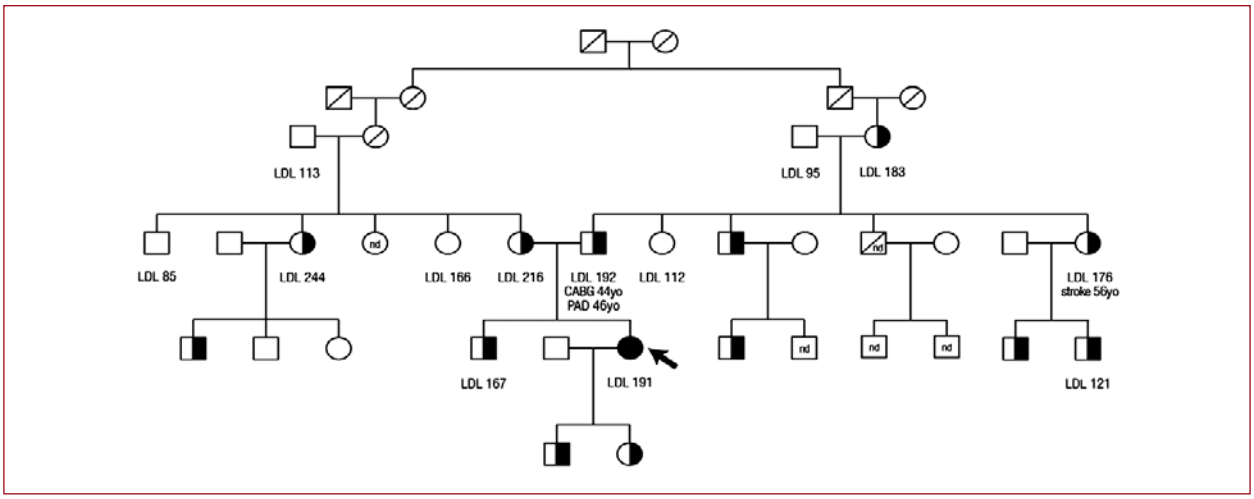


**Figure 1.** Pedigree of family. Numbers indicate low-density lipoprotein cholesterol (LDL-C) in mg/dl
Arrow — proband. Abbreviations: CABG, coronary artery bypass grafting; PAD, peripheral artery disease; nd, no data; yo, years old

due to APOB defect (FDB, familial defective APOB) is rare with a prevalence of 1:1000 and 1:4 000 000 for heterozygous and homozygous, respectively [2]. Homozygotes were observed in populations with the founder effect as well as in descendants of consanguineous parents, which is probably the case [3]. The most common pathogenic variant detected in the *APOB* gene results in reduced LDLR binding capacity, up to 25%, which leads to an accumulation of LDL-C [4]. Only a few cases of patients with homozygous FDB have been described in the literature and this is the first *APOB* homozygote case in the Polish population [2]. Homozygous FH (HoFH) is characterized by severe clinical presentation and classically is defined by LDL-C levels of ≥500 mg/dl in untreated patients, and ≥300 mg/dl in treated subjects with cutaneous or tendinous xanthoma occurring at less than 10 years of age [2]. Patients with pathogenic variants in *APOB* may have a milder clinical presentation, and the present case constitutes a documented example of this. As described in the literature, the average LDL-C concentrations found in cases of homozygous FDB were 265–331 mg/dl, and were lower in younger individuals, which may, at least partially, explain the proband's surprisingly low level of LDL-C [2, 5]. Causes of the relatively low LDL-C levels are sought in the apolipoprotein-E-dependent increased clearance of LDL-C precursor particles and the mechanism of up-regulation of the LDLR [3, 4]. Patients with HoFH do not attain satisfactory results of standard treatment and therapy must often be extended to include PCSK9 inhibitors or LDL-apheresis. The fact that the therapeutic objective is not achieved in patients with HoFH is particularly significant, as they are in the group of very high cardiovascular risk.

The described case of HoFH presented an unusual clinical course, even for FDB individuals, and underlines the necessity of a critical and individual assessment of all subjects with suspected FH.

## *Article information*

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**Conflict of interest:** None declared.

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