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Autosomal recessive hypercholesterolemia in Spanish kindred due to a large deletion in the *ARH* gene

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Abstract

Autosomal recessive hypercholesterolemia (ARH) is a rare genetic defect that causes marked elevation of plasma low-density lipoprotein cholesterol (LDL-C) and premature atherosclerosis. It is due to mutations in the *ARH* gene that plays a critical role in the internalization of LDL receptor (LDLR) in liver cells. We describe a Spanish family where a 24-year-old proband and his 13-year-old sister showed the typical characteristics of ARH. The proband's LDLR activity in peripheral lymphocytes was 14% of normal and his *in vivo* LDL catabolism was reduced by 64% compared to normal. Notably, the sister showed normal lipid levels when her umbilical cord blood was tested. In this family, ARH was due to homozygosity for a large ~1.6 kb deletion that eliminates exon 4 of *ARH* gene. Analysis of *ARH* mRNA demonstrated that the fusion of exon 3 to exon 5 during the splicing of the primary transcript changes the reading frame leading to stop codon 7 amino acids downstream in exon 5. No protein product was detected in affected individuals by immunoblot analysis. This novel mutation adds new support to the molecular heterogeneity of ARH in the Mediterranean basin.
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Severe elevation of plasma low-density lipoprotein cholesterol (LDL-C) is associated with an increased risk of atherosclerosis and is frequently caused by genetic disorders. Several genetic defects leading to severe hypercholesterolemia have been identified [1]. They show different modalities of transmission, but almost all act by impairing the removal of circulating LDL by LDLR-mediated endocytosis in the liver [2].

Recently, a recessive form of severe hypercholesterolemia, defined ARH, has been characterized [3]. ARH resembles to homozygous familial hypercholesterolemia (FH) as affected individuals show markedly elevated LDL-C (typically between 400 and 600 mg/dl) with normal levels of plasma total triglycerides (TG), large and bulky xanthomas and premature onset of coronary artery disease (CAD) [4,5]. In contrast to FH, ARH individuals present reduced LDLR activity in hepatocytes and lymphocytes, but normal or only moderately impaired in fibroblasts [5]. The responsible gene has been located in the chromosomal region 1p36–35 and encodes a novel 308 amino acid adaptor protein (ARH) that contains a PTB domain [6]. We and others have demonstrated that ARH protein is critical for the efficient internalization of LDLR in the liver [6–8].

ARH has been reported in several families of different ethnic origin [6,9–17], but it is particularly common in

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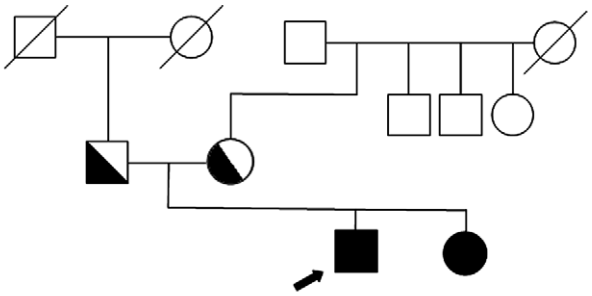
the island of Sardinia where the disease has an estimated frequency of 1 over 40,000 individuals and only two mutations (W22X and c.432insA) account for all reported ARH cases [10]. Taking advantage from this, we recently compared 42 ARH Sardinian patients with 42 well characterized Italian homozygous FH and demonstrated that the clinical phenotype of ARH is milder than that of receptor-negative and resembles that of receptor-defective homozygous FH [18]. We also noted that the risk of CAD is 5-fold lower in ARH compared to patients with receptor-defective homozygous FH [18].

To date, 13 different mutations causing ARH have been described [6,9–16]. The majority of them are predicted to introduce premature stop codons, either as a results of a point mutation or a frameshift [6,9–12,14,15]; one was due to a large ~2–7 exon deletion [9] and another to a 2.6 kb insertion in intron 1 [12]. All reported ARH-causing alleles were associated with the absence of ARH protein except two, where truncated forms of the protein have been detected by Western blot analysis [12,16]. In the present study, we describe the first Spanish kindred with ARH where this disorder was due to a novel mutation consisting in a large ~1.6 kb deletion eliminating exon 4 of *ARH* gene.



Age at time of the study	30	30	4	8
TC (mg/dl)	260	207	606	318
VLDLC (mg/dl)	41.7	23.6	23.3	nd
IDL (mg/dl)	6.3	2.9	23.2	nd
LDLC (mg/dl)	158	149	529	253
HDLC (mg/dl)	54	31.4	31	40
TG (mg/dl)	269	171	115	123
% LDLR activity	57	63	14	nd

Fig. 1. Plasma lipoprotein fractionation, LDLR activity in peripheral lymphocytes in the proband (arrow) and its parents. Plasma lipids in the proband's sister are also reported. Data were obtained in the proband after 1 month drug therapy wash-out and in his sister during 20 mg/day lovastatin treatment. nd = not done.

Materials and methods

Patients

We studied a family from Hinojosa del Duque, a little town in the province of Cordoba (Spain) (Fig. 1). Parents showed no evidence of consanguinity even though all members of their families were born in the same town for at least five generations.

The proband is a 24-year-old man who was first diagnosed with severe hypercholesterolemia (1040 mg/dl) at 4 months of age when he underwent a general biochemical study because of a respiratory disease. At that time, the presence of tuberous xanthomas in knees and heels was recorded. He was prescribed with 12 g of cholestyramine per day and since then plasma total cholesterol (TC) levels ranged between 800 and 350 mg/dl. After his referral to the Lipid Clinic of the University Hospital of Reus in 1987, all causes of secondary hyperlipidemia were preliminary ruled out by the standard clinical tests. Lipoprotein analysis demonstrated that his hypercholesterolemia was due to a severe elevation of LDL-C, while VLDL-C and IDL-C were within the normal range; a reduced concentration of HDL-C was also noted (Fig. 1). His 30-year-old father presented slight elevated plasma levels of LDL-C and TG, while the 30-year-old mother showed a normal lipoprotein profile. Afterwards, measurement of LDLR activity in cultured lymphocytes as well as *in vivo* study of LDL metabolism were also performed as described below. A diagnosis of pseudohomozygous FH was established and liver transplantation was excluded. Lovastatin was first administered and TC levels fell below 350 mg/dl (Fig. 2) and tendon xanthomas disappeared. In the following years, increasing doses of simvastatin, atorvastatin and more recently a combination therapy with atorvastatin 80 mg and ezetimibe 10 mg were prescribed allowing TC to range between 280 and 250 mg/dl (Fig. 2). His weight and height development has been normal and no liver or muscle side effects were noted. An exercise treadmill test performed at the age of 18 was normal.

The proband's sister is a 13-year-old girl. Because of her brother antecedents, a prenatal lipid profile was performed in umbilical cord blood at the 22nd week of pregnancy. TC, HDL-C and apo B were normal (data not shown). However, further measurements at 2 months of age demonstrated severe elevation of TC (1200 mg/dl). Therefore, she

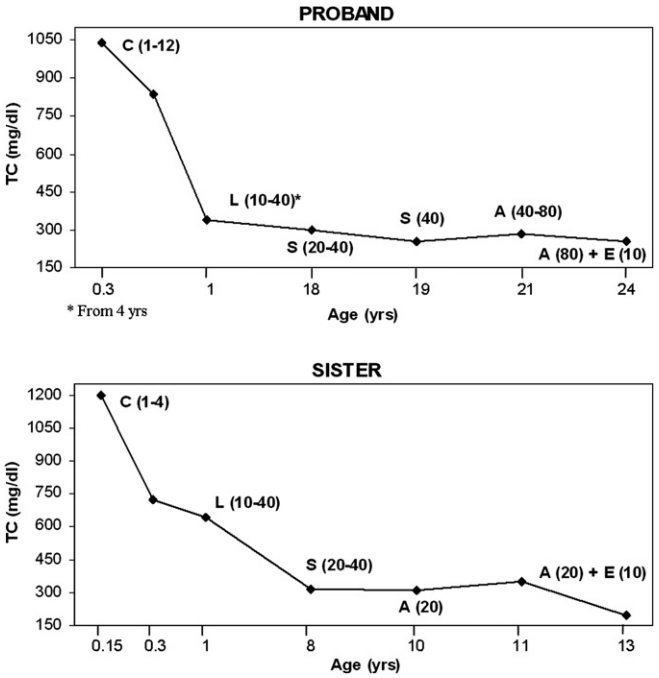


Fig. 2. Changes of total cholesterol (TC) in the proband and his sister (proband 2) during therapy. C, cholestyramine (g/day); L, lovastatin (mg/day); S, simvastatin (mg/day); A, atorvastatin (mg/day); E, ezetimibe (mg/day).

was started on low-dose cholestyramine. At 4 months of age, her TC values were 724 mg/dl and TG 242 mg/dl. At 1 year of age, she started 10 mg lovastatin and henceforward increasing doses of different statins were used. At present, the combination of 20 mg atorvastatin plus

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