Lipoid Proteinosis: Identification of Two Novel Mutations in the Human ECM-1 Gene and Lack of Genotype-Phenotype Correlation

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Sir,

Lipoid proteinosis (LP; OMIM #247100), first described by Urbach & Wiethe in 1929 (1), is a rare autosomal recessive disorder. It is characterized by a hoarse voice and skin and mucosal changes. Beaded papules along the eyelid margins are characteristic, as are infiltration of the oral mucosa. Associated findings include epilepsy, mild mental retardation, respiratory tract obstruction, abnormal dentition and ocular abnormalities. Histological findings include an extensive deposition of amorphous eosinophilic material around capillaries, sweat coils and in the thickened papillary dermis, which stains with periodic acid-Schiff (PAS). Molecular genetic studies of LP consanguineous families have revealed mutations in the ECM1 gene located on 1q21.2 (2, 3). There are three known splice variants: ECM1a, ECM1b and ECM1c, encoding proteins of 540, 415 and 559 amino acids. To date, 41 distinct germline missense, nonsense, splice site, small and large deletions and insertions, have been reported (2–12). Approximately 50% of the mutations cluster to exon 6 and 7 of the gene. We report here two novel mutations and one recurrent mutation in two unrelated patients of German and Arab-Israeli ancestry.

CASE REPORTS AND METHODS

Case 1. A 45-year-old Arab man from Israel, the eldest son of first cousins, presented with longstanding disfiguring nodules and tumours of the skin. Two of his nine siblings had similar disease characteristics, but to a lesser degree, and two others were congenitally deaf. The patient had worked in manual jobs for many years. He noticed that his lesions improved slightly at times of unemployment. His voice had been hoarse since many years. He had worked as a farmer and his intelligence was normal.

RESULTS

Case 1 carried a homozygous deletion of an adenosine at position 1393, at the 5' end of exon 10 (Fig. 1a). The deletion lead to a substitution of the amino acid lysine by asparagine, followed by an early stop codon, which resulted in a 75 amino acid protein truncation (c.1393delA; p.Lys465AsnfsX2). The screening of 60 control cases from unrelated individuals of Arab ancestry failed to disclose the presence of the mutation. In sequencing the ECM1 gene of case 2, two mutations were identified: a c.240delTC in exon 4 and a c.1019delA in exon 7 (Fig. 1b, c). The mutation c.1019delA has been described previously as a homozygous mutation in a Kuwaiti individual with LP (2). The mutations c.240delTC and c.1019delA lead to a frameshifts and premature stop codons 18 and 36 amino acids downstream to the mutations, respectively.

DISCUSSION

The ECM1 protein contains six cysteine doublets, with a CC-(X7–10)-C pattern (13). The cysteine arrangement leads to the formation of double-loop structures, which are involved in protein/protein interactions and therefore are essential for the function of the protein. The ECM1 protein interacts with fibulins 1C and 1D variants, extraacellular matrix components of a wide range of connective tissues and various basement membranes, through its...
The authors declare no conflicts of interest.

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Fig. 1. (a) Homozygous 1393delA in exon 10 of the ECM-1 gene. Upper panel: case 1; lower panel: unrelated control. Arrow represents site of adenosine deletion. (b) Heterozygous 240delTC mutation in exon 4. (c) Heterozygous 1019delA mutation in exon 7 of the ECM-1 gene. (b+c) Upper panel: case 2; lower panel: unrelated control. The circled nucleotides are deleted in a heterozygous state in case 2.