Presence of palmar xanthomas in myotonic dystrophy identifies different patterns of linkage disequilibrium between the apolipoprotein E and myotonic dystrophy protein kinase loci

To the Editor:

Linkage disequilibrium (LD), coinheritance of adjacent alleles at neighboring loci in a population, facilitates the localization of gene variants causing Mendelian disorders and the mapping of complex traits loci through the human genome.[1] We have recently assessed the influence of different patterns of LD between myotonic dystrophy protein kinase (DMPK) and apolipoprotein (apo) E genes on the phenotypic expression of myotonic dystrophy (DM1) and suggest that the presence of planar-palmar xanthomas (Fig. 1) contributes to distinguish between the apo E4-DMPK and apo E2-DMPK allelic combi-

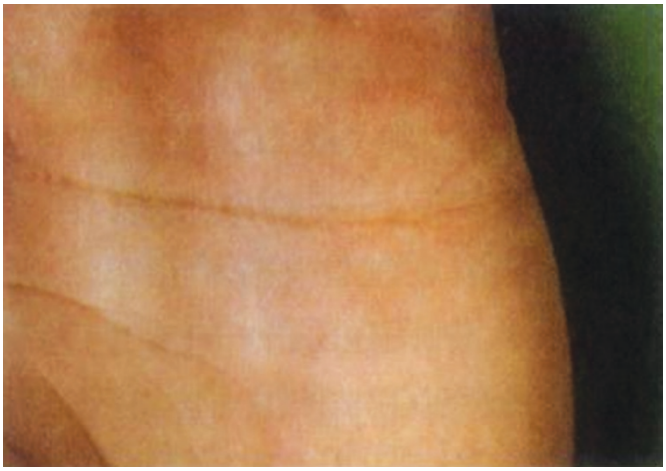

Fig. 1. Palmar xanthomas are characterized by a brownish, yellowish coloration of the palmar striae and are pathognomonic of type III dyslipidemia.

nation. DM1 is an autosomal dominant disorder caused by a $(CTG)_n$ repeat expansion in the DMPK gene.[2–5] The prevalence of DM1 in the Saguenay-Lac-St-Jean founder population (280,000 inhabitants) is one of the highest worldwide (1/500).[6] DMPK clinical expression is pleiotropic and includes myotonia, muscular weakness and atrophy, increased plasma triglyceride (TG) levels, insulin resistance, and several endocrinologic or physiologic disturbances associated with aging.[2,7] Apo E is a constituent of lipoproteins that contributes to the normal variation of lipid concentrations in population. There are three common isoforms of apo E: apo E2, apo E3, and apo E4 (apo E3 being the most frequent).[8] DMPK and apo E genes belong to the same syntenic group on chromosome 19, and there is a well-documented LD between DMPK and the apo E4 allele. Interestingly, we have observed that in DM1 pedigrees where apo E4 is absent, LD tends to shift to the DMPK-apo E2 allelic combination.[9,10] Palmar xanthomas are not a clinical feature of the DM1-apo E4 phenotype but characterize DM1-apo E2. In affected pedigrees, DM1 individuals carrying the E2 allele (heterozygotes or homozygotes) tend to express palmar xanthomas, whereas unaffected apo E2 heterozygotes relatives do not (Fig. 2).

In the general population, palmar xanthomas are a characteristic of type III dysbetalipoproteinemia (type III), an atherogenic lipid disorder characterized by the presence of very low-density lipoprotein (VLDL) remnants [intermediate-density lipoprotein (IDL), β-VLDL] in fasting plasma, hypertriglyceridemia (increased VLDL-cholesterol/TG ratio), palmar-planar and/or tuberous xanthomas, and increased cardiovascular disease risk. In the general population, type III is most frequently associated with apo E2 homozygosity (E2/E2), whereas apo E2 heterozygotes (E2/E3) tend to exhibit a normal lipid profile in absence of additional primary or secondary dyslipidemic factors.[8] In DM1-affected French-Canadian pedigrees, DM1 individuals carrying the E2 allele (heterozygotes or homozygotes) tend to express palmar xanthomas, whereas unaffected apo E2 heterozygotes relatives do not. Our observations suggest that the simultaneous presence of DM1 and apo E2 allele promote type III expression, as shown by the familial evaluation of palmar xanthomas distribution. In this case, the search for palmar xanthomas while performing DM1 patients' physical examination might contribute to specify health status and identify the pattern of LD between DMPK and apo E loci.

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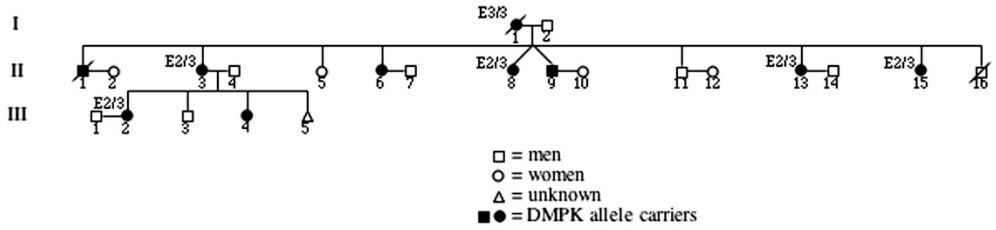

Fig. 2. Lipid profile and apolipoprotein (apo) E polymorphism were analyzed in this sample of 23 related French-Canadians, including 10 myotonic dystrophy (DM1) patients. Subjects gave informed consent to participate in this study and were assigned a code, which systematically denominalizes all clinical data. This project has received the approval of the Chicoutimi Hospital Ethics Committee. VLDL particles were isolated by ultracentrifugation, and the high-density lipoprotein (HDL) was obtained after precipitation of low-density lipoprotein (LDL). Cholesterol and triglyceride (TG) levels were enzymatically measured on a Multiparity Analyzer CX7 (Beckman). Apo E genotype was determined by polymerase chain reaction amplification.[11] In this pedigree, palmar xanthomas and features of type III (presence of β-VLDL, VLDL-cholesterol/TG ratio > 0.5) were observed among DM1-apo E2 heterozygotes individuals, but not among unaffected E2 relatives.

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