A Novel Mutation (c. 1072_1074delGAG) in the α-Galactosidase Gene of a Taiwanese Family with Fabry Disease

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Sir,

Fabry disease (FD; OMIM 301500) is an X-linked recessive inheritance with defective activity of lysosomal enzyme, α-galactosidase A (α-Gal A). Clinical diagnosis is sometimes difficult because of diverse manifestations. Confirmation of the disease is based on enzyme levels as well as on molecular biology. The prognosis is related to renal, cardiovascular and neurological complications (1). We report a deletion mutation (c. 1072_1074delGAG) in exon 7 of α-Gal A gene on Xq22 in a Taiwanese family with Fabry disease. To our knowledge, this mutation has not been described previously in the literature.

CASE REPORT

A 25-year-old Taiwanese man suffered from numerous asymptomatic punctate tiny dark-red papules over the lower back (Fig. 1). Angiokeratoma was confirmed by pathology. In addition, intense generalized aching, particularly in the hands and feet (known as acroparaesthesia), was noted during febrile episodes and higher ambient temperature. Neurological examinations, including vibratory, pinprick, light touch and position sensation modalities, were normal. Ophthalmological examinations revealed cornea verticillata and tortuous conjunctival vasculature. Echocardiogram revealed left ventricular hypertrophy with severe mitral valve regurgitation and possible chordae tendinae rupture. Serum creatinine, blood urea nitrogen and 24-h protein excretion in the urine were within the reference range. The glomerular filtration rate by TC^{99m}-DTPA examination was 70.6 ml/min (lower normal limit 88). Enzyme activity of α-Gal A in plasma was 0.9 nmol/h/ml (normal range 7.6 – 16.5). The proband has one sibling aged 22, who has similar but milder dermatological manifestations. In addition to cornea verticillata and acroparaesthesia, he had hypohidrosis, proteinuria (120 mg/24 h) and ST change on V2-4 leads by ECG. A borderline glomerular filtration rate (89.9 ml/min) and reduced enzyme activity (1.0 nmol/h/ml) were also noted in the sibling. Their mother, a Fabry carrier, had no abnormal findings except cornea verticillata and subnormal enzyme activity (2.6 nmol/h/ml).

The coding regions of the α-Gal A of the proband, his sibling and mother were examined by PCR amplification and sequencing. A deletion c. 1072_1074delGAG (deletion of Glu at codon 358) was found in exon 7 (Fig. 2). No other nucleotide sequence variation was detected after completely sequencing all the coding exons of the α-Gal A gene and their adjacent exon/intron junction sequences.

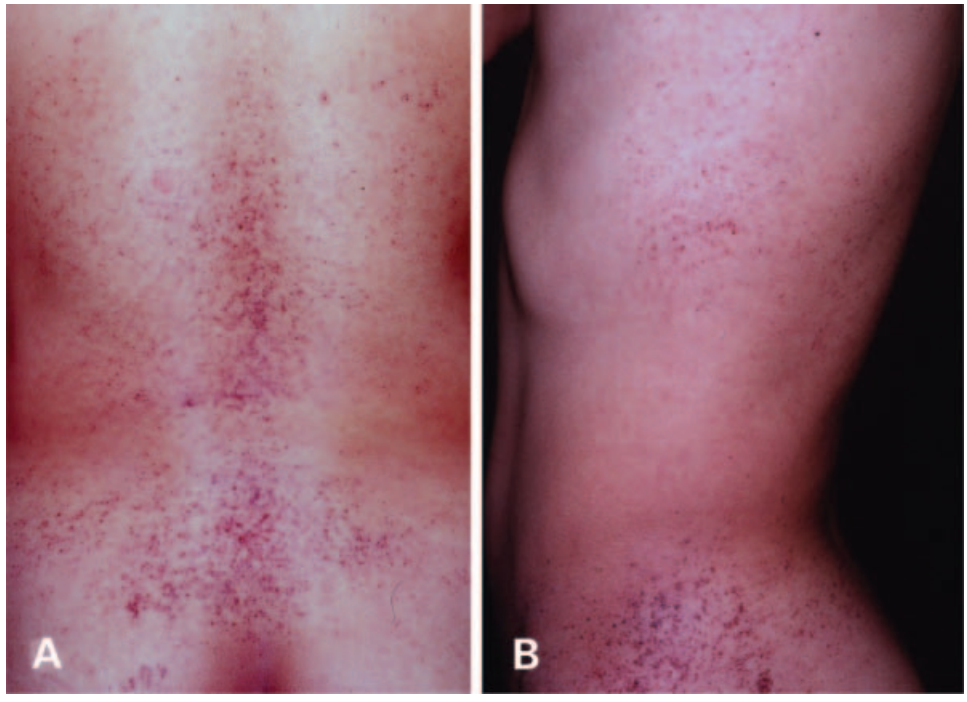

Fig. 1. Numerous asymptomatic punctate tiny dark-red papules over lower back, buttocks and thighs.

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Fig. 2. Sequence flanking the c. 1072–1074delGAG deletion. The deletion of GAG is indicated by the arrow. As a result of deletion, the Glu at codon 358 was deleted.

DISCUSSION

Fabry disease is an X-linked sphingolipidosis caused by complete or partial deficiency of α-Gal A. The enzyme deficiency results in accumulation of globotriaosylceramide (also known as ceramide trihexoside), as well as digalactosyl ceramide and blood group B, B1 and P1 glycolipids in the lysosomes of vascular endothelial, smooth muscle, epithelial and ganglion cells (2). This metabolic defect causes angiokeratomas, painful neuropathy, cardiac and cerebrovascular injury, and renal failure (3). It is a rare disease, mostly reported in Caucasians, with an incidence of 1 in 117,000 live births (4). Because of X-linked inheritance, male patients are predominantly affected, while female carriers can be asymptomatic or affected to a variable degree owing to random inactivation of the X-chromosome. Variable genetic defects have been reported (5). Understanding the relationship between genotype and clinical phenotype will clearly aid in the prognosis, treatment and counselling of patients with Fabry disease, but the results have so far been controversial (6–9). It is interesting to note that phenotypic variations can occur in the same family with identical genetic mutation. Whether the heterogeneous manifestations can be attributed in part to environmental factors has not been determined, but it has been suggested that such phenotypic variations may also be related to blood groups of affected individuals. Patients with blood group AB or B may have a more aggressive disease course owing to a greater body substrate burden (5).

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