GENETICS AND GENODERMATOSES

A PATHOGENIC VARIANT IN ALAS2 SEGREGATED WITH FAMILIAL X-LINKED DOMINANT PROTOPORPHYRIA IN A LARGE MULTI-GENERATIONAL CHINESE FAMILY

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Background: X-linked dominant protoporphyria (XLDPP) is a rare, hereditary hepatobiliary and hematologic disorder characterized by cutaneous photosensitivity, decreased iron stores and increased erythrocyte protoporphyrin.

Objectives: To characterize the clinical features of the first Chinese XLDPP pedigree and to identify the genetic etiology of the condition in the family.

Methods: We ascertained the first multigenerational Chinese family with XLDPP. We observed and described the dermatoscopic
findings of this disorder under dermoscopy, and assessed photo damage in XLDPP patients using the Fotofinder system and very high frequency (VHF) skin ultrasonic system. We performed next generation sequencing and Sanger sequencing to detect and confirm genetic variants in DNA samples from the XLDPP family. Moreover, we monitored the hepatobiliary function as well as hematologic changes in related family members.

Results: A four base pair deletion (c.1706_1709delAGTG, p.E569fs) in ALAS2 (NM_000032.4) was identified in the proband and found to segregate with disease in affected family members in an X-lined dominant pattern. The c.1706_1709delAGTG deletion in ALAS2 is predicted to cause a frame-shift that would lead to the replacement of the last 19 residues in the C-terminal of the ALAS2 enzyme by 24 different amino acid residues, causing elevated ALAS2 enzyme activity. Cutaneous photo damage in XLDPP patients was significantly more severe than that in non-predisposed individuals. In addition, XLDPP patients' hepatobiliary function was significantly impaired and progressively worsened with age. Laboratory test results indicated that affected individuals also had anemia and iron overload.

Conclusions: XLDPP in this pedigree was caused by the likely pathogenic c.1706_1709delAGTG deletion in the ALAS2 gene. Affected members developed photosensitive skin lesions, significantly impaired hepatobiliary function, and hematological anomalies. As expected, hemizygous males were more severely affected than heterozygous

females.