GENETICS AND GENODERMATOSES

NOVEL COMPOUND HETEROZYGOUS MUTATIONS ON EXON 9 AND EXON 10 OF LDLR GENE IN TWO CHINESE SISTERS RESULT IN FAMILIAL HYPERCHOLESTEROLEMIA WITH SEVERE XANTHOMA AND 16 YEARS FOLLOW-UP

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Background: Familial hypercholesterolemia (FH) is a genetic disorder. The homozygous type is rare and severe. Main manifestations include high level of cholesterol and LDL, xanthomas and premature coronary artery disease. Here we reported two compound heterozygous mutations of LDLR gene in two sisters with FH.

Observation: The proband was a 2 years old girl with xanthoma at buttock, Achilles tendons, wrists and elbows for 2 years. The level of cholesterol was 18.3 mmol/L, and LDL-C was 13.26 mmol/L. The histopathologic examination of the lesion on buttock revealed a great number of xanthoma cells at dermis. Four years later, her young sister was born and similar symptoms gradually emerged. Their parents were not consanguineous. The diagnosis was homozygous FH.
Their gene mutations were checked. After genomic DNA extraction from the peripheral blood sample of all subjects (7 pedigree members and 150 unrelated control individuals), the pathogenic mutations were detected by exome sequencing and polymerase chain reaction amplification and direct DNA sequencing. The result revealed two novel compound heterozygous mutations of LDLR gene, i.e., c. 1246C>T at exon 9 (maternal), and c.1448G>A at exon 10 (paternal). The latter one produce a premature termination codon which result in a truncated protein lacking of 378 C-terminal amino acids downstream. Both mutations were observed concurrently only in the two affected sisters. Neither mutation was discovered in 150 unrelated Chinese control individuals. They were treated with rosuvastatin unregularly.
After 16 years of follow-up observation, the xanthomas have grown tremendously and plasma cholesterol levels have significantly changed.

Key message: Two mutations were the pathogenic mutations, which were first found compounded and induce giant xanthoma.