Next-generation Sequencing Identified a Novel EDA Mutation in a Chinese Pedigree of Hypohidrotic Ectodermal Dysplasia with Hyperplasia of the Sebaceous Glands

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Hypohidrotic ectodermal dysplasia (HED) is one of approximately 200 different genetic conditions of ectodermal dysplasia (ED) identified by the lack, or dysgenesis of, at least 2 ectodermal derivatives, such as hair, nails, teeth and sweat glands (1, 2). The hereditary model in most cases is X-linked (XLHED) caused by mutations localized in the gene encoding ectodysplasin-A (EDA) (1, 3, 4). Less commonly, HED caused by mutations localized in the ectodysplasin-A receptor (EDAR) or ectodysplasin-A receptor-associated adapter protein (EDARADD) gene with an autosomal dominant or autosomal recessive pattern of inheritance. XLHED (OMIM: 305100) is characterized by a triad of signs of hypohidrosis, hypotrichosis and hypodontia. This study enrolled a single Chinese family with XLHED with the rare phenotype of remarkable hyperplasia of the sebaceous glands and performed next-generation sequencing (NGS) to scan for potential mutations.

CASE REPORT

A Chinese pedigree of HED was collected. The proband was a 27-year-old male who reported absence of sweating, dry thin lustreless sparse hair over the scalp, absence of eyelashes, axillary, pubic and whole-body hair, and congenitally missing teeth (Fig. 1a,b). He also reported intolerance to heat. In particular, the patient had hundreds of solid, whitish yellow, milia-like papules distributed symmetrically over his whole face in confluent plaques, which had been present since puberty (Fig. 1b). A vellus hair was present in the centre of each papule. The patient had a prominent forehead and a saddle nose. The oral mucosa, nails and palmoplantar surfaces were roughly normal, except for dry skin. Histological findings from the scalp included the absence of anagen hair follicles and sweat glands (Fig. 1d). Biopsy of the papules on the face showed many large sebaceous gland lobules surrounding vellus hair follicles and the absence of sweat glands (Fig. 1e).

NGS was performed as reported. Written informed consent was obtained from all subjects and approval for the study was provided by the Institutional Review Board and the ethics committee of No. 1 Hospital of China Medical University. Genomic DNA from the proband’s peripheral blood was random fragmented, and the targeted exon sequences plus flanking sequences (all exons extending 100 bps on each side of an exon) of EDA, EDAR and EDARADD genes were specifically captured and enriched using an array-based hybridization chip (NimbleGen, Madison, WI, USA). Sequencing was performed on the HiSeq2500 (Illumina, San Diego, CA, USA) sequencer using 90-bps paired-end chemistry according to standard operating protocols. Single nucleotide polymorphisms (SNPs) and indels were identified using the SOAPsnp and GATK Indel Genotyper, respectively.

The mean of the targeted area of EDA, EDAR and EDARADD was 155.43×. A mean of 95.3% of base pairs with >30× coverage were successfully detected. Six variants were detected. The frequency of the deletion variant (EDA: EX6 DEL) was 0 in SNPs database and it was predicted as candidate mutation (Fig. S1a1). The other 5 variants (EDAR c.1109T>C, EDAR c.1056C>T, EDAR c.1056T>C, EDAR c.1056T>G, EDAR c.1056A>C) were successfully detected. The other 5 variants (EDAR c.1109T>C, EDAR c.1056C>T, EDAR c.1056T>C, EDAR c.1056T>G, EDAR c.1056A>C) were successfully detected. The other 5 variants (EDAR c.1109T>C, EDAR c.1056C>T, EDAR c.1056T>C, EDAR c.1056T>G, EDAR c.1056A>C) were successfully detected.

Fig. 1. (a) Clinical appearance of the proband. (b) Numerous papules in confluent plaques symmetrically distributed on his face. (c) Notable improvement after treatment with fractional CO2 laser. (d) Skin biopsy of the scalp revealed a complete loss of sweat glands (haematoxylin and eosin (HE) ×100). (e) Histological presentations of a skin biopsy from his face showed many large sebaceous gland lobules (HE×100). Written permission was given by the patient to publish these photographs.