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Case Report (Pages: 6899-6902)

Autosomal Recessive Hypohidrotic Ectodermal Dysplasia Caused by a Novel Mutation in *EDAR* Gene

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Abstract

Backgrounds
Hypohidrotic ectodermal dysplasia (HED) is a rare genetic disorder, distinguished by hypotrichosis, hypohidrosis, and hypodontia. HDE can be inherited in X-linked recessive manner as a result of mutations in the *ectodysplasin A (EDA)* gene as well as autosomal dominant and autosomal recessive manners both of them caused by mutations in *EDA receptor (EDAR)* and *EDAR-associated death domain (EDARADD)* genes.

Results
In this report, we investigated a consanguineous Iranian family with autosomal recessive form of HED. A homozygous missense mutation was detected in exon 1 of *EDAR* gene in the proband (c.278C>G) resulting in p.C93S that alters the sequence of the EDAR protein.

Conclusion
We facilitated the effective genetic counseling and prenatal diagnosis in this family through detection of the disease causing mutation.

***Key Words*:** Ectodermal dysplasia, EDAR, Mutation.

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1- INTRODUCTION

Hypohidrotic ectodermal dysplasia (HED) is a rare genetic disorder, distinguished by hypotrichosis (abnormal development of scalp and body hair), hypohidrosis (Impaired sweating), and hypodontia (congenital absence of teeth) (1, 2). HDE is mostly inherited in X-linked recessive manner (OMIM: 305100) as a result of mutations in the *ectodysplasin A (EDA)* gene (3). However, HDE can be inherited in autosomal dominant (OMIM: 129490), and autosomal recessive manners (OMIM: 224900) both of them caused by mutations in *EDA receptor (EDAR)* and *EDAR-associated death domain (EDARADD)* genes (4, 5).

Proteins that encoded by these three genes are essential for the activation of the Nuclear factor-κB (NF-κB) signaling pathway, a necessary pathway for normal development of ectodermal organs both in humans and in mice (6). Moreover, mutation in two other genes named *WNT10A* and *TRAF6* have been shown to cause HDE (7).

2- CASE REPORT

In this report, we investigated a consanguineous Iranian family with autosomal recessive form of HED. The proband was a male child aged 7 years with light-colored, brittle, and slow-growing hair. Eyebrows were scanty and skin was dry and scaly. He suffered from hypohidrosis and hypodontia. The teeth were small and pointed. He showed a characteristic facial dysmorphology including a prominent forehead, a flattened bridge of the nose, and thick lips (**Figure.1**). Other features include thin, dark-colored skin around the eyes and chronic skin problems such as eczema. In order to find the underlying genetic cause, genomic DNA was isolated from blood sample of the patient after informed consent using the standard salting out technique.

Whole exome sequencing was performed in Laboratory of Molecular Diagnosis, University of Leuven using Illumina sequencer. A homozygous missense mutation was detected in exon 1 of *EDAR* gene (c.278C>G) resulting in p.C93S that alters the sequence of the EDAR protein. This mutation has not been reported in generalist polymorphism databases (ExaC or exome variant server [EVS]) or the 1000 genome database (http://www.1000genomes.org/1000-genomes-browsers). *In silico* functional analysis of the sequencing results by Polyphen -2 (Polymor-phism Phenotyping v2) showed that it is possibly damaging.

In addition, Combined Annotation Dependent Depletion (CADD) which applies a uniform, genome-wide, variant scoring metric (C-score) through combining Sorting Intolerant From Tolerant (SIFT) method and PolyPhen to predict the pathogenicity of any variant (8), showed that this nucleotide change is deleterious with a score of 27. The mutation was confirmed by Sanger DNA sequencing in patients. Segregation analysis showed that parents were heterozygous for the detected mutation.

3- DISCUSSION

In this study we detected a novel homozygous missense mutation in *EDAR* gene in an Iranian consanguine family affected to autosomal recessive HED. EDAR belongs to tumor necrosis factor receptor superfamily (TNFRSF) and is a transmembrane protein with three cysteine-rich domain (CRD) in the ectodomain. These CRDs are rich in cysteines, are constrained by disulfide bridges and are involved in the receptor-ligand interaction (1, 2). According to Human Gene Mutation Database (HGMD) (www.hgmd.cf.ac.uk/), 42 different HED-causing mutations in *EDAR* gene have been reported up to now, 36 of which are missense mutations

(http://www.hgmd.cf.ac.uk/ac/gene.php?gene=EDAR). The detected mutation in the present study (c.278G>C) is a missense mutation in CRD2 that disrupts a disulfide bridge existing between cys93 and cys113 (http://www.uniprot.org/uniprot/Q9UNE0) and most probably alters the protein's secondary structure and ⁄or the ligand binding interaction site resulting in impairment of NF-ƙB signaling which is important in the development of ectoderm. Interestingly, two other missense mutation in cys87 and cys113 has been reported in CRD2 disrupting its two disulfide bridges and causing HED phenotype (3, 4).

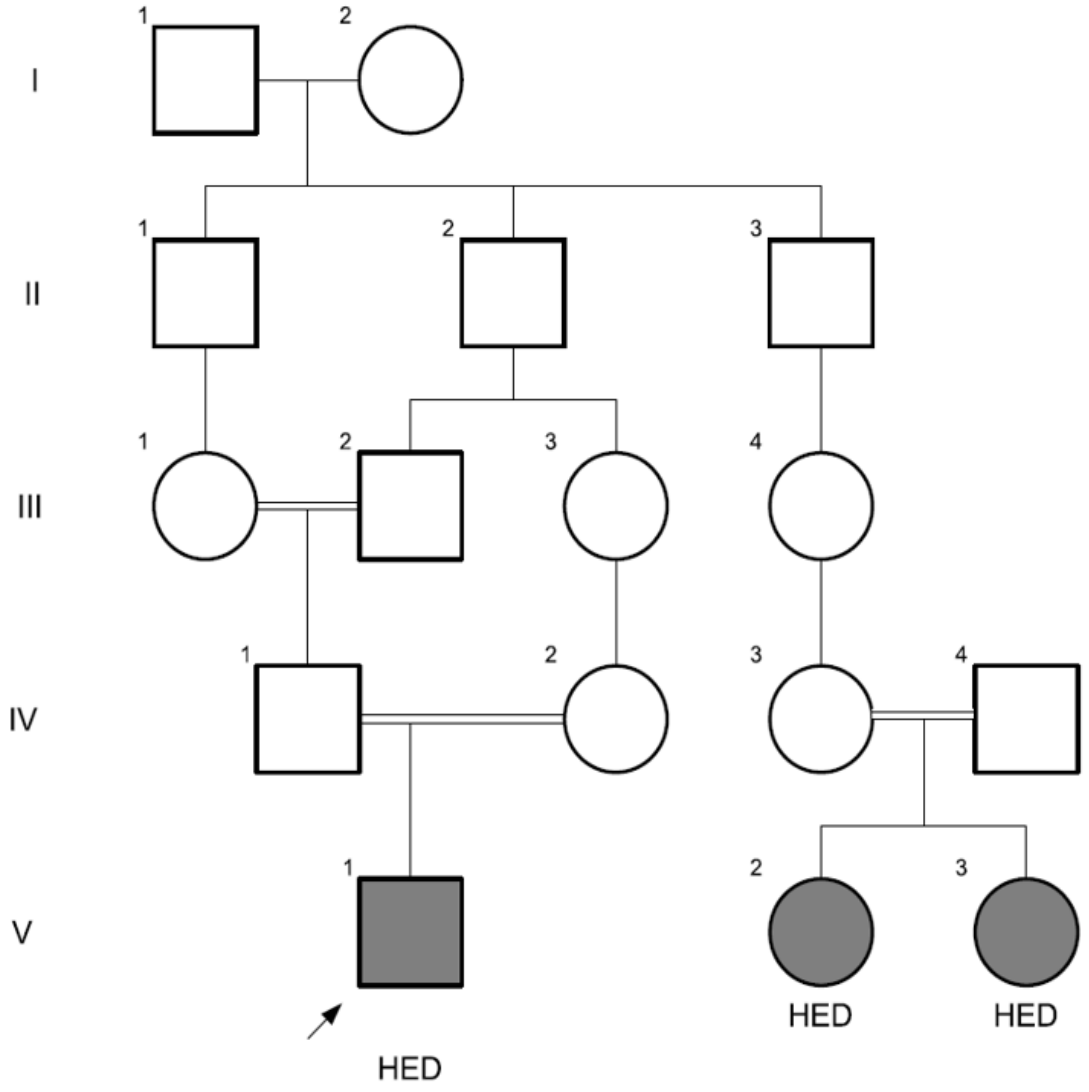

Fig. 1: The pedigree of family with hypohidrotic ectodermal dysplasia (HED).

4- CONCLUSION

In conclusion, we have reported the sixth missense mutation in CRD2 and added to *EDAR* mutation repository. Identification of underlying genetic cause of inherited disorders would facilitate preimplantation genetic diagnosis as well as prenatal diagnosis. In addition, detection of carrier status of parents enables genetic counselor to provide recurrence risk in each family.

5- CONFLICT OF INTEREST: None.

6- ACKNOWLEDGEMENT

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