

# A *CDH3* Mutation is Segregated in an Iranian Family with Congenital Hypotrichosis and Juvenile Macular Dystrophy

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### Abstract

### **Backgrounds**

Hypotrichosis with juvenile macular dystrophy (HJMD) is a rare genetic disorder caused from mutations in the *Cadherin 3 (CDH3)* gene.

### Results

In the present study, we reported an Iranian family with three affected members born to a consanguineous parent. Mutational analysis using whole exome sequencing has revealed a nucleotide change in *CDH3* gene (NM\_001793:exon8:c.830delG) which leads to a frame-shift mutation (p.G277Afs\*20). No intra-familial phenotypic variation was found.

### Conclusion

Identification of disease-causing mutation in this family facilitated the effective genetic counseling and prenatal diagnosis.

### Key Words: Cadherin-3, Gene, Mutation.

<u>\*Please cite this article as</u>: Ghafouri-Fard S, Fardaei M, Bagher Tabei SM, Dianatpour M, Miryounesi M. A CDH3 Mutation is Segregated in an Iranian Family with Congenital Hypotrichosis and Juvenile Macular Dystrophy. Int J Pediatr 2018; 6(1): 6999-7002. DOI: **10.22038/ijp.2017.27276.2350** 

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Received date: Aug.10, 2017; Accepted date: Aug. 22, 2017

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# **1- INTRODUCTION**

Hypotrichosis with juvenile macular dystrophy (HJMD) is a rare genetic disorder caused from mutations in the Cadherin 3 (CDH3) gene which codes Pcadherin (1, 2). P-cadherin is expressed in retinal pigment epithelium (RPE) together with E-cadherin (3). The first report of cooccurrence of juvenile macular dystrophy hypotrichosis congenital and was published in 1935 (4). Afterwards, several cases of association between these two distinct phenotypes have been published (5-8). However, the underlying genetic cause was unclear till 2001 when Sprecher et al. through homozygosity mapping in four consanguineous families mapped the gene on chromosome 16q22.1 (1).

Mutation analysis of HJMD patients has resulted in identification of several CHD3 mutations up to now. The first identified mutation has been a homozygous deletion in exon 8 of the CDH3 gene (1). Subsequently, Indelman et al. detected a missense mutation (R503H) in all affected members of a family with HJMD (2). Afterwards, other mutations have been detected in CHD3 gene in patients affected with HJMD from diverse ethnic backgrounds (9). Notably, CDH3 mutations have also been associated with another syndrome consisted of hypotrichosis, macular dystrophy, ectodermal dysplasia and ectrodactvly (EEM Syndrome) (10). Here we present a consanguineous Iranian family with HJMD.

# **2- CASE REPORT**

Here we present an Iranian family with three affected members referred to Shiraz Comprehensive Medical Genetics Center, Shiraz University of Medical Sciences, Iran. Their pedigree is presented in **Figure.1**. All three patients were full term

with no perinatal complications. All of them suffered from reduced visual acuity and hypotrichosis. They complained from progressive deterioration of visual function which was started from teenage years. Ophthalmologic examination with indirect ophthalmoscope had shown abnormalities in the posterior pole. Fundus examination demonstrated primary involvement of the macular region. The pattern of hair was normal at birth but hypothricosis was apparent around 4 months of age. After puberty, they had fractional regrowth of short and thin hair. There was no other dermatologic complication apart from mild eczema. No developmental delay was reported in cases. No other abnormality has been detected in affected members.

In order to find the underlying mutation, DNA was extracted from blood samples of patients after obtaining written informed consent. Whole Exome Sequencing (WES) carried out using paired-end was sequencing method with 100X coverage in Illumina HiSeq4000 (Laboratory for Molecular Diagnosis, University of Leuven, Belgium). Afterwards, bioinformatics analysis of the sequencing data was performed using international and standard bioinformatics databases Combined software. Annotation Dependent Depletion (CADD) was used for scoring the deleteriousness of detected nucleotide changes (11). The detected mutation was confirmed by Sanger sequencing.

A homozygous mutation was found in CDH3 gene (NM 001793:exon8:c.830delG) which frame-shift leads to a mutation (p.G277Afs\*20) and is pathogenic based ClinVar database on (https://www.ncbi.nlm.nih.gov/clinvar/). As its CADD score is 34, it is predicted to be highly pathogenic.

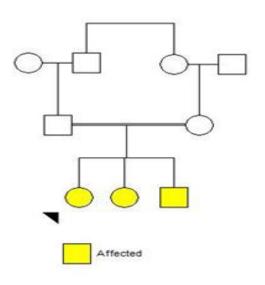


Fig.1: The family pedigree demonstrates three affected members.

## **3- DISCUSSION**

We have detected a previously reported mutation in *CDH3* gene in an Iranian family affected with HJMD (NM\_001793:exon8:c.830delG). This mutation leads to production of a truncated fusion protein with a premature stop codon at amino acid residue 295. This protein is predicted to be deficient in intracellular and membrane spanning domains as well as extracellular cadherin repeats (10).

Notably, it has been associated with both HJMD in a Turkish family (9) and EEM syndrome in a Brazilian family (10). A recent study has also confirmed the association of this mutation with inherited retinal disease using whole-genome sequencing (12). The patients presented in current study. did the not have characteristic features of ectodermal defect such as partial anodontia, absence deformities of digits, ectrodactyly and syndactyly (10) except for hypothrichosis. So, we describe them as having HJMD

rather than EEM syndrome. Future studies are needed to assess if these so-called distinct syndromes are the same disorder at diverse areas of a severity spectrum. In addition, the wide spectrum of phenotypes associated with a single mutation should be considered in genetic counseling of affected families as well as prenatal diagnosis.

## **4- CONCLUSION**

Similar mutations might be associated with distinct phenotypes of HJMD and EEM syndrome. Gene-gene interactions or environmental factors might modulate the phenotypic characteristics in each family.

## **5- CONFLICT OF INTEREST:** None.

### **6- ACKNOWLEDGMENT**

The authors are grateful to the patient's family for their participation in the study.

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