EDA mutation as a cause of hypohidrotic ectodermal dysplasia: a case report and review of the literature

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ABSTRACT. Ectodermal dysplasia (ED) represents a collection of rare disorders that result from a failure of development of the tissues derived from the embryonic ectoderm. ED is often associated with hair, teeth, and skin abnormalities, which are serious conditions affecting the quality of life of the patient. To date, a large number of genes have been found to be associated with this syndrome. Here, we report a patient with hypohidrotic ED (HED) without family history. We identified that this patient’s disorder arises from an X-linked HED with a mutation in the EDA gene (G299D) found by whole-exome sequencing. In addition, in this paper we summarize the disease-causing mutations based on current literature. Overall, recent clinical and genetic research involving patients with HED have uncovered a large number of pathogenic mutations in EDA, which might contribute to
a full understanding of the function of EDA and the underlying mechanisms of HED caused by EDA mutations.

Key words: Hypohidrotic ectodermal dysplasias; Whole exome sequencing; EDA

INTRODUCTION

The ectoderm is one of the three germinal layers established during embryogenesis, and is important for the development of sweat glands, hair, nails, nerves, and enamel. Although ectodermal dysplasias (EDs) are not common human disorders, over one hundred and fifty different types of congenital defects of certain ectodermal structures and their accessory appendages, which can be divided into 11 clinical subgroups, have been reported to date (Sepulveda et al., 2003). The subtype of hypohidrotic ED (HED) is the most common form, and is estimated to affect 1 in 100,000 newborns (Keller et al., 2011). The severity of HED has been found to vary between different patients. HED might result in considerable social and psychological problems and is also a source of great financial burden for affected families (Norderyd, 2012). However, there have not been any effective and economic methods for the treatment of HED worldwide until recently (Ioannidou-Marathiotou et al., 2010). Evidence suggests that HED is a typical genetic disease, and currently at least 5 genes have been found to be associated with HED (Cluzeau et al., 2011). Therefore, HED-related gene screening and prenatal gene diagnosis are necessary for affected individuals. Recently, some studies have been indicated that whole-exome sequencing represented an economic and effective tool for the diagnosis of genetic diseases for patients with or without family history as the cost of high throughput sequencing continues to decrease. Here, we report a patient with HED without family history carrying an EDA mutation identified by whole-exome sequencing, and we present a review of the literature of HED caused by EDA mutations.

MATERIAL AND METHODS

Case presentation

The affected boy, 7 years of age, was seen at the Key Laboratory of Guilin 181st Hospital for genetic counseling with the chief complaint of abnormal appearance and an absence of teeth. The boy presented with features of HED and had been diagnosed when he was two years old by other physicians. On our physical examination, it was observed that he had thin and scanty hair, nearly absent eyebrows, and his skin was smooth and dry with small wrinkles. The boy was found to have three teeth erupted in the oral cavity on intraoral examination; radiographic examination confirmed that two teeth were still emerging, and the roots of the erupted teeth were very short and conical (Figure 1). The boy found it difficult to tolerate hot summery days, and his parent revealed that the boy used to live under the air conditioner in summer to combat the heat. A biopsy of abdominal skin stained by hematoxylin-eosin in Shenzhen People’s Hospital indicated the presence of a few lymph cells infiltrated into the dermis, but no sweat glands, hair follicles, sebaceous glands, or other skin appendages were found (Figure 2). The couple also indicated that no family history of HED was present and that no features of HED had been ever identified in other family members during routine physical examinations.
Mutation analysis

In order to identify the genetic type of HED, blood sample was obtained from the affected boy, and standard cytogenetic and molecular procedures were performed. We sequenced the whole exome of the affected boy according to our previous study (Sui et al., 2013). The variants were called and filtered by the National Center for Biotechnology Information (NCBI) dbSNP Build 132, the 1000 Genomes Project, HapMap, and the YH database. And the candidate mutation was confirmed by conventional Sanger sequencing.
RESULTS

Karyotype analysis with G banding showed that the affected boy was a normal male. The mean depth of the target region was 148.24X, and the whole-exome sequencing identified a mutation in \textit{EDA} (NM_001399.4: c.896G>A, p.G299D), which was a previously reported mutation associated with HED, conventional Sanger sequencing confirmed that the mutation was not present in the affected boy's parent or in our 3 normal control. Based on the clinical features, the result of biopsy, whole-exome sequencing, and the literature of HED, we suggest that \textit{EDA} (G299D) might be a disease-related mutation in this affected Chinese boy.

DISCUSSION

HED (MIM 305100) is the most prevalent form of ED. Given the high complexity of developmental control during embryogenesis, it is expected that considerable genetic heterogeneity underlies HED. To date, molecular research has shown that 64 genes and 3 chromosomal regions are involved in EDs (Visinoni et al., 2009). Among these, \textit{EDA}, \textit{EDAR}, \textit{EDARADD}, \textit{TRAF6}, \textit{WNT10A}, and \textit{NEMO} (or \textit{IKKG}) have been found to be associated with HED (Cluzeau et al., 2011), with \textit{EDA}, \textit{EDAR}, \textit{EDARADD I}, and \textit{WNT10A} accounting for 90% HED, and \textit{EDA} mutations identified in more than 50% HED (Cluzeau et al., 2011).

\textit{EDA} is also known as \textit{ED1}, \textit{HED}, \textit{EDA1}, \textit{HED1}, \textit{ODT1}, \textit{XHED}, \textit{ECTD1}, \textit{XLHED}, and \textit{STHAGX1}. Its product, ectodysplasin-A (EDA), was found to be a member of the tumor necrosis factor (TNF) superfamily of ligands. EDA contains a transmembrane domain, putative furine cleavage site, collagen subdomain, and a TNF-homologous domain. In the literature, over 100 different variations in \textit{EDA} have been reported in patients with or without EDs. Although a great number of the \textit{EDA} mutations might represent null mutations and thus be without clear genotype-phenotype correlation (Mikkola, 2009), at least 82 variations have been identified as pathogenic mutations associated with HED in the NCBI ClinVar database (http://www.ncbi.nlm.nih.gov) and in published papers (Table 1) (Pääkkönen et al., 2001; Schneider et al., 2001; Cluzeau et al., 2011). In addition, \textit{EDA} mutations have been found in patients with EDs worldwide, including in India, Brazil, and China (Schneider et al., 2001; Visinoni et al., 2009; Cluzeau et al., 2011). In the spectrum of deleterious \textit{EDA} mutations, the most frequent event was found to be missense mutations; followed by deletions and nonsense mutations causing premature truncation of the EDA protein; the rest of the mutations were shown to affect splice sites or represent in-frame deletions (Pääkkönen et al., 2001). From the structure of the EDA protein and of the reported mutations, we find that the majority of residues affected by missense mutations occur in the TNF homology domain, collagen domain, and the furin recognition sequences (Schneider et al., 2001). In our patient, the mutation (G299D) is in the TNF homology domain, and the residue is located in an amino acid sequence which is absent in the EDA-A2 protein. Some studies have indicated that the mutations associated amino acid in the known TNF-like ligands were highly conserved (Pääkkönen et al., 2001). Mutation of G299D might therefore affect receptor binding, and result in an interruption of the interactions of EDA with both EDAR and XEDAR, which might play important roles in the EDA-NF-kB pathway (Aradhya and Nelson, 2001; Kurban et al., 2010). In the literature, the ectodysplasin/NF-kB and Wnt/β-catenin pathways are well known to be involved in the early steps of the development of ectodermal appendages (Figure 3) (Clauss et al., 2008), and it has been hypothesized that the rest of the hitherto unknown mutations related to HED might lie in proteins contained in either of these two pathways (Gat et al., 1998; Cluzeau et al., 2011).
Table 1. EDA mutations found in patients with HED in the literature.

<table>
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<tr>
<th>No.</th>
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<th>Variant type</th>
<th>Predicted protein changes</th>
<th>Predicted effect on protein (domain)</th>
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<td>p.?</td>
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<td>p.?</td>
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Continued on next page
HED can be diagnosed by three cardinal features: hypotrichosis (sparseness of scalp and body hair), hypohidrosis (reduced ability to sweat), and hypodontia (congenital absence of teeth) (Wright et al., 2014). For the majority of patients with HED caused by homozygous mutation of EDA, the classic symptoms can be found after infancy, such as peeling skin, periorbital hyperpigmentation, heat intolerance, and uncommonly elevated body temperatures (Blüschke et al., 2014).

Table 1. Continued.

<table>
<thead>
<tr>
<th>No.</th>
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HED = hypohidrotic ectodermal dysplasia.

Figure 3. Overview of EDA involvement in the development of ectodermal appendages (Clauss et al., 2008).
However, diagnosis might be delayed until their teeth fail to erupt or erupt abnormally at the expected age, as seen in our patient who was not diagnosed until two years of age. For female carriers with heterozygous mutations of *EDA*, their features on clinical examination might be mild; for example, including some sparseness of the hair, sweat dysfunction in some part of the skin, and a small number of missing or abnormal teeth (Cambiaghi et al., 2000). Phenotypes associated with *EDA* mutations vary, and might present in the clinic ranging from nonsyndromic hypodontia to classic HED. Some studies have indicated that most pathogenic *EDA* mutations causing nonsyndromic hypodontia were missense mutations associated with the TNF domain; and a great number of pathogenic mutations causing HED were thought to be loss of function mutations (Cambiaghi et al., 2000). In our patient, although the mutation in EDA (G299D) is a missense mutation in the TNF domain, the affected boy has a classic form of HED; therefore, the residue associated with the mutation might interrupt the interaction between EDA and EDAR, thereby impairing its role in the EDA-NF-kB pathway.

For genetic counseling, HED related gene screening is needed. In the literature, Sanger sequencing and multiplex ligation-dependent probe amplification have been commonly used for *EDA* mutation discovery in both research and clinical studies (Lexner et al., 2008). Recently, whole-exome sequencing has been reported to be an economical and rapid tool for genetic diagnosis, and it has been used to diagnose types of disorders similar to ED (Haghighi et al., 2013). In this study, we performed whole-exome sequencing to screen ED-associated genes in a boy affected with HED, and identified that an EDA (G299D) mutation might be the primary cause of the disorder in this patient. This finding demonstrated that whole-exome sequencing is well developed and might be a useful tool for ED-associated mutation identification in patients with HED with or without family history.

In summary, genetic studies involving patients with HED have uncovered a large number of pathogenic mutations in *EDA*, which might be helpful to establish a full understanding of the function of *EDA*. In addition, whole exome sequencing might be useful to identify the type of ED in clinical practice. However, HED is a highly complex and heterogeneous disease. Therefore, genotype-phenotype correlation in different patients needs to be a focus of further research.

**Conflicts of interest**

The authors declare no conflict of interest.

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EDA mutation as a cause of HED


