First Genetically Confirmed X-linked Hypohidrotic Ectodermal Dysplasia in Nepal: Diagnostic Odyssey and Mismanaged Hyperthermia

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ABSTRACT

Hypohidrotic ectodermal dysplasia is a rare inherited disorder affecting ectoderm-derived tissues and is characterized by hypohidrosis, hypotrichosis, and hypodontia or oligodontia. We report the first molecularly confirmed case of X-linked hypohidrotic ectodermal dysplasia in Nepal. An 8-year-old boy from Kohalpur presented with recurrent fever since infancy, inability to sweat, sparse scalp hair, and severe oligodontia. Targeted exome sequencing identified a hemizygous pathogenic variant in the ectodysplasin A gene (c.466C>T; p.Arg156Cys), while no pathogenic variants were detected in the ectodysplasin A receptor or the ectodysplasin A receptor–associated death domain. His sister had mild dental anomalies, suggesting a symptomatic carrier phenotype. This case highlights the value of molecular diagnosis in confirming clinically suspected hypohidrotic ectodermal dysplasia, enabling accurate genetic counseling, family screening, and appropriate long-term management. It also demonstrates the feasibility of advanced genetic testing in Nepal through international laboratory collaboration.

Keywords: EDA gene; Ectodermal dysplasia; Genetic; Hypohidrotic; X-linked recessive

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INTRODUCTION

Ectodermal dysplasia (ED) comprises a heterogeneous group of more than 160 inherited disorders characterized by abnormal development of ectoderm-derived structures, including the hair, teeth, nails, and sweat glands.[1] Hypohidrotic ectodermal dysplasia (HED), also known as Christ-Siemens-Touraine syndrome, is the most common subtype, accounting for approximately 90% of cases.[2] Most cases are inherited in an X-linked recessive pattern due to pathogenic variants in the ectodysplasin A (EDA) gene, which encodes ectodysplasin-A, a protein essential for ectodermal development during embryogenesis.[2,3] In Nepal, the diagnosis of HED has largely been based on clinical features because access to molecular genetic testing remains limited.[4] We report the first molecularly confirmed case of X-linked HED in Nepal, highlighting the importance of genetic diagnosis for accurate counseling and clinical management.

CASE PRESENTATION

An 8-year-old male from Kohalpur, Banke, Nepal, was referred to our facility for evaluation of recurrent fever and dental abnormalities. The clinical history revealed a “diagnostic odyssey” beginning in early infancy. The parents noted frequent episodes of hyperpyrexia during the summer months, which required aggressive cooling with wet towels and fans. The patient had received recurrent courses of antibiotics for these episodes of hyperthermia, which were repeatedly misattributed to infectious causes by local healthcare providers. The child never exhibited visible sweating, even during intense physical exertion. Additionally, the patient had chronic xerosis and difficulty with mastication due to severe dental agenesis. The patient's timeline unfolded as follows: during infancy, recurrent unexplained fever began alongside noted anhidrosis; in early childhood, delayed dental eruption occurred with peg-shaped primary teeth, and at seven years, the child consulted multiple regional hospitals for fevers and was mismanaged as an occult infection, receiving multiple courses of broad-spectrum anti-

biotics for hyperthermia despite negative infectious workups; and at the age of 8 years (current presentation), referred to us that led to clinical suspicion of HED that was followed by molecular confirmation as shown in Figure 1.

Figure 1: An 8-year-old male with hypohidrotic ectodermal dysplasia showing hypotrichosis, frontal bossing, and peg-shaped conical teeth

The family history revealed that the patient was a product of a non-consanguineous marriage. The mother was asymptomatic, but the elder sister exhibited mild dental abnormalities (oligodontia), suggesting symptomatic heterozygous carrier status as shown in Figure 2.

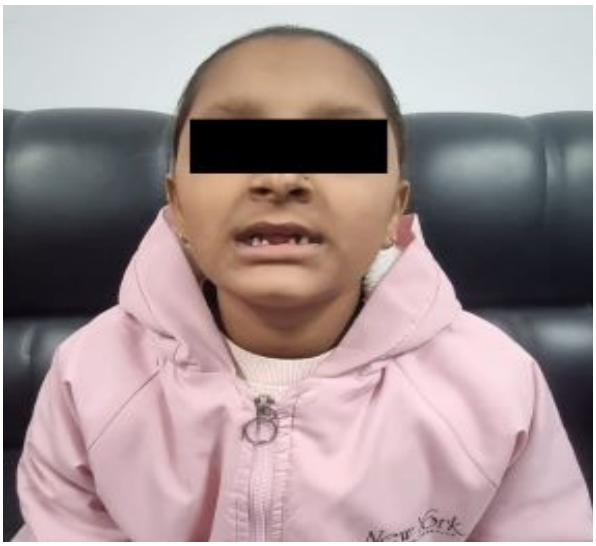

Figure 2: Elder sister showing mild dental anomalies consistent with heterozygous carrier status in X-linked hypohidrotic ectodermal dysplasia

Physical examination revealed that the child's weight and height were below the 10th percentile. Craniofacial assessment revealed frontal bossing, a depressed nasal bridge (saddle nose), and periorbital hyperpigmentation with fine wrinkling. The scalp and body hair were sparse, fine, and hypopigmented. Intraoral Examination revealed severe oligodontia, with only four conical teeth in the maxillary arch and two in the mandibular arch, all of which exhibited hypoplastic enamel.

Initial laboratory investigations (CBC, thyroid function, and renal function) were normal. An orthopantomogram confirmed the absence of multiple permanent teeth. Abdominal and pelvic ultrasonography showed no organomegaly. Peripheral blood samples were collected and sent to a reference laboratory for targeted exome sequencing.

Molecular analysis identified a hemizygous missense mutation in exon 3 of EDA gene (c.466C>T, p.Arg156Cys). No pathogenic variants were detected in EDAR or EDARADD, confirming X-linked HED.

DISCUSSION

The identification of this case as the first genetically confirmed diagnosis of HED in Nepal represents a critical advancement in the country's rare-disease infrastructure. Historically, patients in South Asia have faced a protracted "diagnostic odyssey," characterized by an average delay of 4–5 years and numerous misdiagnoses. Notably, this patient received recurrent courses of antibiotics for episodes of hyperthermia that were misinterpreted as infectious fevers, when they were actually physiological failures of thermoregulation, highlighting a common clinical pitfall in resource-limited settings. This case underscores that, while HED can be suspected phenotypically, molecular confirmation is the only way to exclude autosomal mimics and provide accurate genetic counseling.[1,5]

The p. Arg156Cys variant identified in our patient is a well-documented pathogenic mutation located within the furin protease recognition site of ectodysplasin-A.[6,7] The EDA gene encodes a type II transmembrane protein that must be proteolytically cleaved by furin to release its biologically active C-terminal fragment which is a soluble homotrimer belonging to the tumor necrosis factor (TNF) superfamily. Arginine 156 is an evolutionarily highly conserved residue, and its substitution with cysteine (a neutral, slightly polar amino acid) disrupts the stability and efficient processing of the EDA precursor, without the release of a functional soluble ligand. This pathway is essential for mediating epithelial-mesenchymal interactions that trigger the formation of ectodermal appendages, including hair follicles, eccrine glands and teeth.[3]

Interestingly, the c.466C>T mutation occurs at a CpG dinucleotide, which is a known mutational hotspot owing to the high frequency of spontaneous deamination of methylated cytosine to thymine. This explains why the p. Arg156Cys variant has been reported in HED cohorts across diverse global populations including Mexican, Chinese, and Jordanian families.[5] The severity of the phenotype in our patient, complete anhidrosis, and severe oligodontia confirmed that this variant acts as a severe loss-of-function allele.

In this case, pedigree analysis demonstrated a typical X-linked recessive transmission. Although the mother was asymptomatic, the patient's sister exhibited mild dental anomalies. This

"manifesting heterozygote" phenotype in female carriers is frequently attributed to random X-chromosome inactivation (lyonization).

During early embryogenesis, one X chromosome is randomly inactivated in each cell. If a high proportion of cells in the developing dental lamina or sweat glands have the wild-type allele inactivated, a partial clinical phenotype emerges. Molecular confirmation was vital for this family to understand that the sister had a 50% probability of passing the mutation to her own offspring, allowing for proactive reproductive planning.[8] The management of HED requires a lifelong, multidisciplinary approach involving pediatrics, dermatology, and dentistry. In Nepal, where environmental temperatures often exceed 30°C, thermal regulation is the highest priority. Because the patient lacks the ability to cool via evaporation, the use of water sprays, frequent hydration, and environmental modifications are life-saving. Long-term dental rehabilitation is equally critical; the underweight status of our patient was directly linked to masticatory challenges from oligodontia.[9] A staged plan involving interim prostheses and future dental implants is essential to restore both nutritional intake and psychological well-being.

A major limitation of this case was the need to send samples across international borders owing to a lack of local genomic facilities. This reflects the "service fragmentation" often cited as a top challenge for rare disease patients globally. Furthermore, early molecular diagnosis is becoming increasingly critical as science enters an era of prenatal therapy. Experimental protein replacement therapy using a recombinant Fc-EDA molecule (ER004) successfully restored sweat gland function in human fetuses when administered intra-

amniotic injection.[10] As these therapies move toward commercialization, identifying candidates in resource-limited regions will become a primary ethical and logistical challenge. This report is the first molecular confirmation of X-linked HED in Nepal. The successful identification of the p.Arg156Cys variant underscores the role of collaboration in bridging the diagnostic gaps. Early genetic confirmation remains vital for implementing life-saving interventions and providing families with accurate genetic counseling in resource-limited settings.

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