First Report of X-Linked Hypohidrotic Ectodermal Dysplasia with a Hemizygous c.1142G >C in the EDA Gene: Variant of Uncertain Significance or New Pathogenic Variant?

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Case report

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Titolo: First report of X-linked hypohidrotic ectodermal dysplasia with a hemizygous c.1142G >C in the EDA gene: Variant of Uncertain Significance or new pathogenic variant?

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ABSTRACT

Background

Hypohidrotic Ectodermal Dysplasia (HED) is a genetic disorder which affects structures of ectodermal origin. X-linked hypohidrotic ectodermal dysplasia (XLHED) is the most common form of disease. XLHED Is characterized by hypotrichosis, hypohydrosis and hypodontia. The cardinal features of classic HED become obvious during childhood.

Identification of a hemizygous EDA pathogenic variant in an affected male confirms the diagnosis.

Case presentation

We report on a male newborn with the main clinical characteristics of the X-linked HED including hypotrichosis, hypodontia and hypohidrosis. Gene panel sequencing identified a new hemizygous missense variant of uncertain significance (VUS) c.1142G >C (p.Gly318A1a) in the EDA gene, located on the X chromosome and inherited from the healthy mother.

Conclusion

Despite the potential functional impact of VUS remains uncharacterized, our goal is to evaluate the clinical potential consequences of missense VUS on EDA gene. Given the proband's phenotype compatibility with classic HED, it is reasonable to attribute a causative role to the variant found in hemizygosis in the gene EDA. The present case demonstrates that this novel VUS could broaden the spectrum of genes mutations involved in the HED phenotype.

Background

Ectodermal dysplasia (ED) includes a large and heterogeneous group of rare congenital conditions with structural and functional abnormalities in various tissues originating from the ectodermal layer of the developing embryo. Pinheiro and Freire-Maia defined as ED any condition with lack or dysgenesis of at least two of the ectodermal derivatives: hair, nails, teeth or eccrine sweet glands [1, 2]. The term ED has been used to describe around 200 different clinical conditions. The birth prevalence is estimated around 7 cases in 10,000 live births [1, 3].

The two most common forms of the disease are hypohidrotic/anhidrotic ED (Christ–Siemens–Touraine Syndrome) in which the sweat glands are either absent or significantly reduced in number and hidrotic ED (Clouston syndrome) in which the sweat glands are normal. [4, 5]. Hypohidrotic ectodermal dysplasia (HED) is characterized by a triad of signs comprising sparse hair (hypotrichosis), abnormal or missing teeth (anodontia or hypodontia), and inability to sweat (anhidrosis or hypohidrosis). [6, 7]

Typical clinical manifestations also include dryness of the skin, eyes, airways, and mucous membranes presumably due to the defective development of several exocrine glands. HED can be associated with dysmorphic features (forehead bumps, rings under the eyes, everted nose and prominent lips) and occasionally with absent nipples [8, 9].

Hypohidrotic ED may be inherited as X-linked, autosomal dominant, and autosomal recessive patterns. Four genes (EDA, EDAR, EDARADD, WNT10A) account for 90% of

hypoidrotic/anhidrotic ectodermal dysplasia cases [10, 11]. X-linked hypohidrotic ectodermal dysplasia (XLHED) is the most common form of disease. The EDA gene, located at Xq12-q13.1 and encoding the transmembrane type II ectodysplasin-A (EDA) protein, which belongs to the tumor necrosis factor superfamily, is responsible for XLHED through EDA-EDAR (EDA receptor)-EDARADD (EDAR-associated death domain) pathway. [12, 13].

The function of EDA protein in pathways regulating ectodermal development, is a key regulator of hair follicle and sweat gland initiation. Normally EDA is expressed in ectodermal tissues; it is implicated in epithelial-mesenchymal interactions during ectodermal morphogenesis and odontogenesis [13, 14]. Various mutations in EDA account for vast majority of XLHED cases. The most frequent mutation type is the missense/nonsense which consists of single base-pair substitutions in coding regions [12, 15].

We report on a three month-old boy with XLHED showing a novel hemizygous missense variant of uncertain significance (VUS) in the EDA gene, detected by Next Generation Sequencing (NGS).

Case report

A three-month-old, caucasian boy infant was referred to our observation due to decreased sweating, dry skin and absence of hair on the scalp. Family history for inherited diseases was unremarkable.

He was the second child of healthy non-consaguineous parents. He was born by spontaneous delivery after normal pregnancy, with no birth-related and perinatal complications. APGAR scores were 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 2390 g (4th centile), length 47 cm (12th centile), and head circumference 33 cm (19th centile).

Physical examination showed scaphocephaly, prominent forehead, forehead bumps, rings under the eyes, hypertelorism, epicanthic fold, everted nose, depressed nasal bridge and prominent lips. Both the upper and lower eyelids showed sparse eyelashes. The hair on the scalp and the eyebrows were absent. The skin was thin, pale, dry and exfoliating with eczematous dermatitis widespread,

especially in the scalp. The skin from around the eyes and mouth showed linear wrinkled and was hyperpigmented. (Fig. 1) The parents reported dryness of eyes. Neuromotor and mental development index score of Bayley II scale were normal.

Ultrasound screening did not detect anomalies and routine ECG and echocardiogram evaluation were normal.

Molecular genetic studies were performed on genomic DNA extracted from peripheric blood, through Next Generation Sequencing (NGS). A multigene Ectodermal dysplasia panel, that included EDA, EDAR, EDARADD, EDA2R, TRAF6, NFKBIA, CDH3, WNT10A, was performed. The analysis revealed the hemizygous variant, NM_001399.4: c.1142G >C (p.Gly318A1a) in EDA gene located on the X chromosome. The variant was tested for familial segregation showing heterozygous maternal state.

We established a multidisciplinary follow-up: ophtalmologic evaluation, hearing screen and visual evoked potentials were normal at five months.

The following physical examinations showed delayed teeth eruption: only two small, conical canines were present at fifteen months.

The last clinically evaluation was performed at twenty-four months of age, with persisting poor weight gain (3^{th} centile), reduced ability to sweat, heat intolerance, chronic eczematous rash especially on the face, wrinkled periorbital skin with Dennie-Morgan infraorbital fold.

Intraoral examination revealed severe oligodontia with only two conical anterior teeth eruption previously described and a wide midline diastema. (Fig. 2)

Orthodontic management was planned in order to improve the limited chewing function ability.

Neuropsychomotor follow-up and mental development index score of Bayley II scale were in the normal range for the age.

Discussion and conclusions

The molecular pathogenesis of HED is not yet fully understood. *EDA* is the gene responsible for X-linked HED [6]. Classic HED is often diagnosed after infancy in patients showing typical hypotrichosis, hypohidrosis, and hypodontia. In the male proband the diagnosis of classic HED was established with the above characteristic features. The identification of a hemizygous EDA pathogenic variant or biallelic *EDAR*, *EDARADD* or *WNT10A* pathogenic variants confirmed the diagnosis [6, 16].

EDA mutations had been considered as genetic conditions, without a clear genotype-phenotype correlation [15, 17]. Burger and Schneider (2014) suggested a reproducible association of common EDA genotypes with XLHED phenotypes. A systematic mapping of EDA mutations with an evaluation of quantifiable clinical data may help to distinguish the pathogenetic gene mutations with respect to those allowing a residual ectodysplasin A activity [15, 18]. A multigene panel also including *EDA*, *EDAR*, *EDARADD*, *WNT10A* may be useful for the differential diagnosis.

Different pathogenic variants including nucleotide substitutions (missense, nonsense, and splicing), small deletions and insertions, and gross deletions have been identified in *EDA* [16, 19]. Pathogenic variants in *EDA* lead to ectodysplasin A molecules that are unable to regulate epithelial-mesenchyme interactions, resulting in abnormal ectodermal appendages. Several pathogenic variants in *EDA* produce ectodysplasin A that is unable to be converted to their active forms and mediate the cell-to-cell signaling regulating the morphogenesis of ectodermal appendages [20, 21]. The missense variant reported in our study is novel and does not result among those reported in the International literature (PubMed/Medline), in the Catalog of Human Genes and Genetic Disorders (OMIM), in the Genome Aggregation, ClinVar and in The Human Gene Mutation Database. According to the American College of Medical Genetics and Genomics this genetic variant is currently considered VUS.

VUS may or may not be disease-causing or associated with increased risk of an abnormal phenotype; the identification of a variant of uncertain significance does not confirm or exclude a diagnosis. A VUS does not meet the criteria to be classified as pathogenic or benign [22].

We analyzed the variant in silico by using software Scale-Invariant Feature Transform (SIFT), DANN, DEOGEN, MutationTaster, for the prediction of possible deleterious variants in human proteins. Combined Annotation Dependent Depletion (CADD), another algorithm used to help assess the potential pathogenicity of a variant, display scores for this variant of 26,9. Despite the variant reported in our study has been described as VUS with an imprecise potential functional impact, the prediction tools used suggest a potential pathogenetic effect.

To our knowledge, this is the first report of a VUS in a XLHED and it may be demonstrate that a mutation of the EDA gene caused by a hemizygous variant, c.1142G >C on the X chromosome, can lead to the XLHED clinical spectrum. Therefore, in consideration of the proband phenotype, a causative role of the variant found in hemizygosis in the gene EDA cannot be excluded.

Furthermore, only male hemizygotes are affected by this X-linked disease, being the heterozygous females clinically normal, as it happens in the vast majority of XLHED cases accounting for gene mutation.

In conclusion, despite we know many genetic variations involved in the development of HED, the latest investigation techniques such as NGS could increase our knowledge about genetic etiology.

Present patient seems to demonstrate that his clinical phenotype is due to the c.1142G >C (p.Gly318A1a) mutation in EDA gene. This novel VUS could broaden the spectrum of genes mutations involved in the development of HED.

The identification of this new mutation may contribute to evaluate the genotype/phenotype correlations. We deemed it useful to describe and characterize a novel mutation of EDA because we hope that a great number of further studies on the effect of normal and abnormal function of EDA protein will lead to a better knowledge of this group of ED. Future studies are mandatory to elucidate genomic and epigenomic susceptibility factors, which could cause mutations on EDA gene.

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Availability of data and materials

The clinical data used during the current report are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Author's contributions

GA, MF, GM drafted the manuscript and participated in management of the case. TM and GLB managed the case. CG coordinated the study and participated in its design. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for pubblication

Written informed consent was obtained from the patient's parents for publication of this report and any accompanying images. A copy of the written consent is available for review.

Figures

Fig. 1. X-linked hypohidrotic ectodermal dysplasia. (a) missing eyebrows, sparse eyelashes; (b) scaphocephaly, missing hair, eczematous dermatitis

Fig. 2. Severe oligodontia. Two conical anterior teeth and a wide midline diastema.

Figures

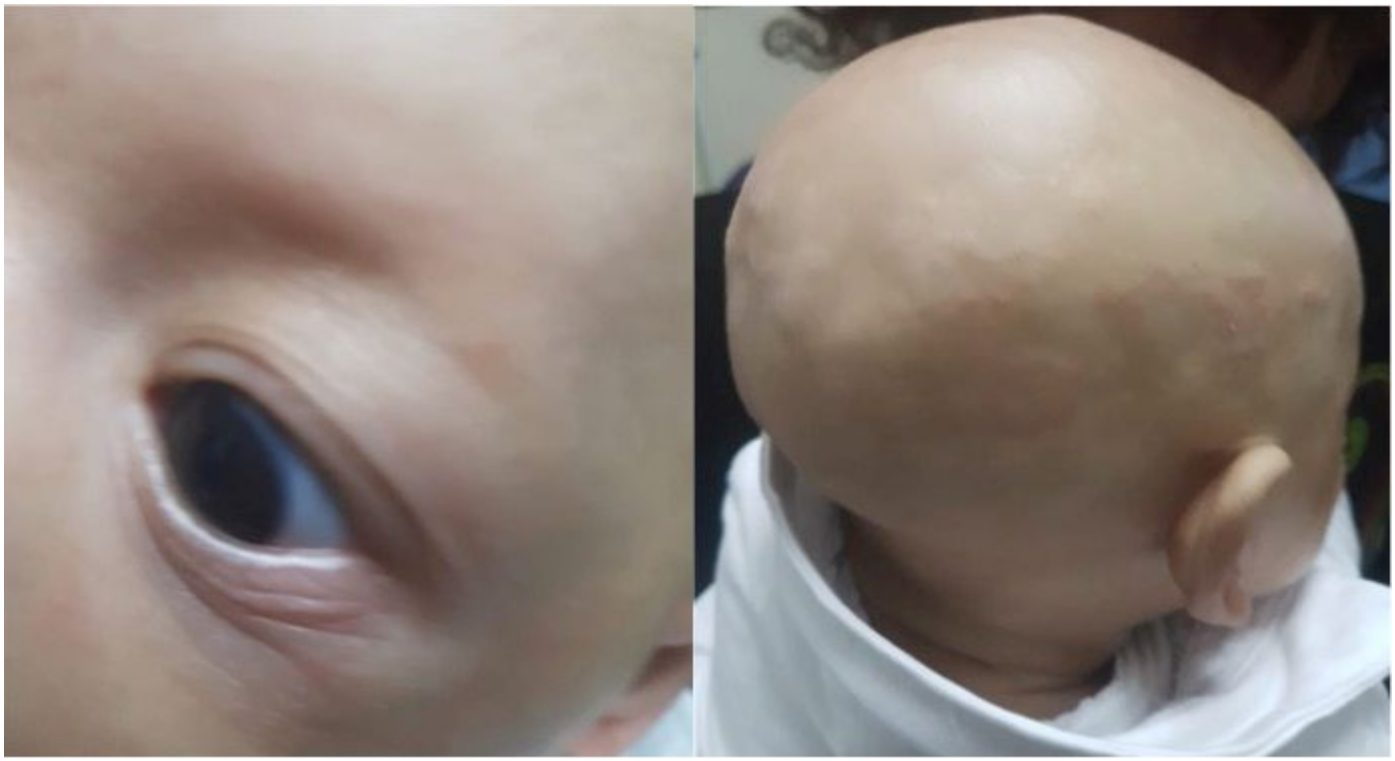

Figure 1

X-linked hypohidrotic ectodermal dysplasia. (a) missing eyebrows, sparse eyelashes; (b) scaphocephaly, missing hair, eczematous dermatitis

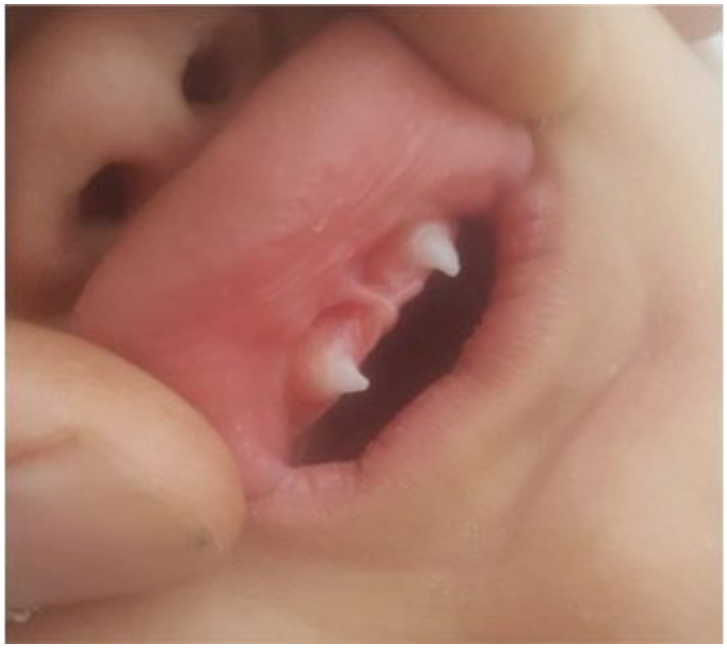

Figure 2

Severe oligodontia. Two conical anterior teeth and a wide midline diastema.