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Hypohidrotic Ectodermal Dysplasias: Phenotypic and Genotypic Findings in 32 Cases

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ABSTRACT

Hypohidrotic ectodermal dysplasias are a genetic condition affecting ectoderm-derived structures such as hair, teeth, nails, and sweat glands, resulting from variations in the *EDA*, *EDAR*, *EDARADD*, and *WNT10A* genes. This study examined 32 cases from 25 unrelated families from Türkiye, identifying seven novel variants in the *EDA*, *EDAR*, and *WNT10A* genes. The distribution of genetic alterations across the cohort revealed that 44% of the families (11/25) harbored variants in EDA, whereas EDAR and WNT10A variants were identified in 32% (8/25) and 24% (6/25) of families, respectively. Clinical evaluation revealed the characteristic hypohidrotic ectodermal dysplasia triad of hypotrichosis, hypodontia, and hypohidrosis was observed in 87.5% of cases, along with other symptoms such as dry skin, atopic dermatitis, and developmental delays. All cases presented with hair, eyebrow, and eyelash abnormalities, ranging in severity from subtle thinning to marked hypotrichosis. Among the cohort, one case exhibited severe atopic dermatitis as the predominant symptom. Targeted next-generation sequencing and clinical exome sequencing were employed to determine the genetic basis of the condition, emphasizing the importance of early diagnosis for targeted interventions. This study expands the genetic and phenotypic spectrum of hypohidrotic ectodermal dysplasia, presenting a comprehensive overview of molecular findings and genotype–phenotype correlations in the population from the Turkish population.

1 | Introduction

Ectodermal dysplasias (ED) are a heterogeneous group of genetic disorders characterized by the abnormal development of at least two ectoderm-derived structures, including hair, teeth, nails, and sweat glands. Single gene defects with different inheritance patterns are detected in ED. Hypohidrotic ectodermal dysplasia (HED) is the most common type of ED and has a prevalence estimated at 2.8–2.99 in 100 000 [1–4]. HED is clinically defined by a triad of symptoms: sparse or absent hair (hypotrichosis), dental anomalies (such as hypodontia, oligodontia, or conical teeth), and impaired sweat gland function (hypohidrosis), which may lead to episodic hyperthermia. Characteristic craniofacial features include frontal bossing, periorbital wrinkling, sparse/absent eyelashes and eyebrows, a saddle and small nose, prominent lips, hypodontia/adontia, conical teeth, and taurodontism.

In newborns with classical HED, heat intolerance, peeling skin, and periorbital hyperpigmentation may be observed, while delayed tooth eruption or conical teeth, along with hypotrichosis, hypohidrosis, and hypodontia, typically become evident during childhood.

Clinical findings of HED encompass episodic hyperthermia resulting from reduced ability to sweat, recurrent respiratory tract infections attributed to intense basal secretions, atopic eczema, and dry skin [5, 6]. Additional features include hypotrichosis characterized by fine, sparse, blonde, and slow-growing hair, a hoarse voice caused by laryngeal mucosa dryness, and gastroesophageal reflux. *EDA*-related HED is characterized by X-linked inheritance. In contrast, biallelic or monoallelic pathogenic/likely pathogenic variants in *EDAR*, *EDARADD*, and *WNT10A* genes are associated with autosomal recessive and autosomal dominant inheritance patterns, respectively. Within the genetic spectrum of HED, *EDA* constitutes the most frequently mutated gene (~50%–60%), followed by *EDAR* (~10%–15%) and *WNT10A* (~15%–20%), with *EDARADD* (~2%–3%) being the least commonly involved. On the other hand, genetic etiology cannot be revealed in approximately 10% of the cases [1]. While classical type HED can be easily diagnosed with clinical findings in childhood, the clinical findings of mild type HED may be more subtle.

In 2019, Wright et al. proposed a classification of ectodermal dysplasias (EDs) based on molecular pathways, emphasizing the roles of the EDA/NF-κB and WNT signaling pathways in the pathogenesis of hypohidrotic ectodermal dysplasia (HED) [7]. The classification was revised in 2022 by Peschel et al. to reflect recent advances in the field [8]. The *EDA* gene encodes ectodysplasin, a type II membrane protein implicated in signaling processes essential for ectodermal organogenesis. EDA functions as a ligand of the tumor necrosis factor (TNF) superfamily. Its receptor, ectodysplasin-A receptor (EDAR), is a transmembrane protein that contains domains homologous to the TNF receptor family. The structural homology between these two molecules suggests that EDA and EDAR act as a receptor–ligand pair. Furthermore, the *EDAR* and *EDARADD* genes encode components of a TNF-like signaling cascade that activates downstream NF-κB pathways [9–11]. Similarly, *WNT10A*, a member of the WNT gene family, is critical for embryonic tissue differentiation (Figure 1) [12]. Notably, the EDA/NF-κB and WNT/β-catenin pathways demonstrate a dynamic interplay, with the former maintaining WNT10A expression and the latter inducing EDAR expression, highlighting their coordinated role in embryogenesis [13].

To date, 355 variants in the *EDA* gene, 72 variants in the *EDAR* gene, 11 variants in the *EDARADD* gene, and 92 variants in the *WNT10A* gene have been cataloged in The Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/) [14].

Early diagnosis remains critical to prevent the potential mortality and morbidity that hypohidrosis may cause. Genetic diagnosis facilitates proper genetic counseling to identify family members at risk, to apply the preimplantation genetic diagnosis option, to treatment options that can be applied in the intrauterine period, and to new clinical trials.

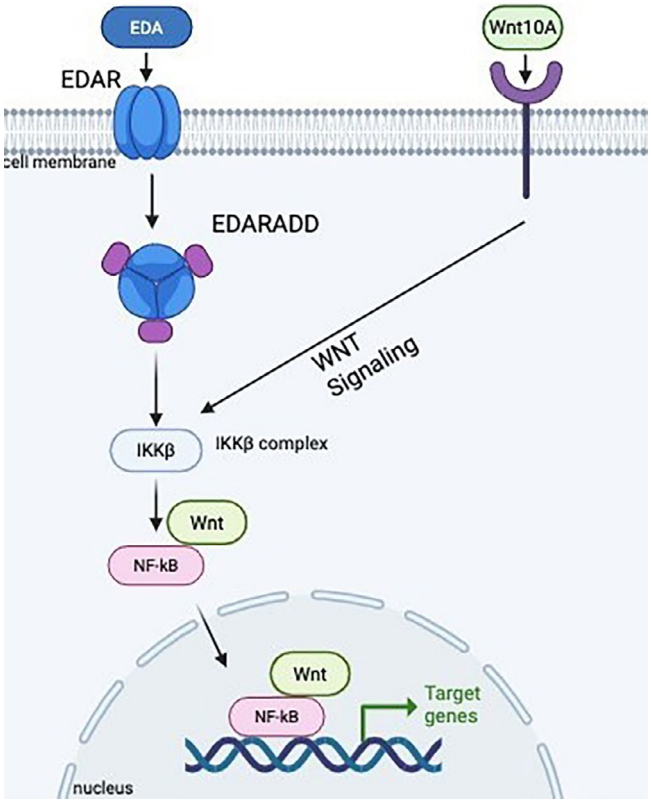

FIGURE 1 | EDA binds to the EDAR receptor on the cell surface, initiating intracellular signal transduction. EDAR activates the IKK complex in the cytoplasm through the adaptor protein EDARADD. This activation allows NF-κB to translocate into the nucleus and induce the expression of target genes. In parallel, WNT10A contributes to IKK activation and supports the signaling process. [Colour figure can be viewed at wileyonlinelibrary.com]

We report seven novel variants in the *EDA*, *EDAR*, and *WNT10A* genes identified in a cohort of 32 patients from 25 families in Türkiye, aiming to contribute to the expanding knowledge of the molecular and variant spectrum of hypohidrotic ectodermal dysplasia. In addition, 11 variants in the *EDA* gene, 7 variants in the *EDAR* gene, and 3 variants in the *WNT10A* gene identified in our cohort have previously been reported in the HGMD (HGMD Professional 2025.x).

2 | Patients and Methods

2.1 | Clinical Evaluation

Our study included 32 cases from 25 unrelated families in Türkiye. The cases were retrospectively selected from patients with ectodermal dysplasia who were referred to the Department of Medical Genetics and found to carry variants in *EDA*, *EDAR*, *EDARADD*, or *WNT10A* genes between 2021 and 2023. Referrals were made from 14 clinical genetics clinics across Türkiye to Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital for re-evaluation of clinical and molecular data. Medical and family history, symptoms, prenatal and natal complications, and developmental milestones were evaluated. Pedigree analysis of at least three generations was drawn; consanguinity and similar or different genetic disorders in family members were investigated.

Clinical examination focused on the skin, teeth, hair/eyelashes/eyebrows, nails, and voice.

2.2 | Molecular Investigation

Genomic DNA was automatically isolated using the spin column method on the QIAcube device (Qiagen, Germany) using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) with 200 μL blood samples taken from the patients. For DNA concentration analysis, measurements were made with a Qubit (Thermo Fisher Scientific, USA) fluorometer. Two different methods were used. The first one was targeted next generation sequencing for four genes. Encoded exons and exon-intron regions of the *EDA*, *EDAR*, *EDARADD*, and *WNT10A* genes were sequenced using next generation sequencing technology (MiSeq, Illumina Inc., San Diego, CA, USA). Sanger sequencing data were analyzed with Integrative Genomics Viewer software (IGV). The second one was clinical exome sequencing. The clinical exome sequencing study was performed with Illumina NextSeq 500/550 using the SOPHiA DDM Clinical Exome Solution v3 kit. CES data was analyzed with Sophia DDM V4. All variants were classified according to ACMG [15]. MutationTaster (https://www.mutationtaster.org/) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) tools were used for in silico predictive analysis. Family segregations were studied with the next generation sequencing method. Segregation data were analyzed with IGV. Variants reported in databases such as HGMD (https://www.hgmd.cf.ac.uk/ac/index.php) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), all variants with a minor allele frequency (MAF) of less than 1% in the gnomAD v2.1.1 (https://gnomad.broadinstitute.org/) database were evaluated. The consent forms were taken from the parents. Ethics committee approval for our study was received from Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Scientific Research and Publication Ethics Board in accordance with the Declaration of Helsinki (85, 07.06.2024).

2.3 | Statistical Analysis

Data were analyzed with IBM SPSS Statistics 22. Gaussian distributions were evaluated with the Shapiro–Wilk test. Statistical significance was defined as a p-value less than 0.05.

3 | Results

Among a total of 32 cases, 14 *EDA* (11 families), 11 *EDAR* (8 families), and 7 *WNT10A* (6 families) cases were identified. The genders of the cases were 13 female (13/32, 40.62%) and 19 male (19/32, 59.37%). The median age at genetic diagnosis was 84 (4–420) months. The median age of *EDA* cases was 66 (12–420) months. The median age of *EDAR* cases was 60 (4–336) months. The mean age of *WNT10A* cases was 159.71 (±31.92) months. Parental consanguinity was detected in 13 families. The triad of HED was presented in 28 cases (28/32, 87.5%). Dental abnormalities were observed in 30 of the 31 cases; in one case, dental evaluation was not possible because the patient was too young. Dry skin was present in 30 out of 32 patients (93.75%). Normal sweating patterns were observed in three cases (Cases 9, 14 and 32). In one case, severe atopic dermatitis was the most prominent symptom. Palmoplantar hyperkeratosis was detected in 4 cases (4/32, 12.5%). All patients had hair-eyebrow-eyelash abnormalities ranging from mild to severe. Nail signs were observed in 15 patients (15/32, 46.87%). Dry eyes were reported in 11 out of 28 evaluable patients (39.28%). Data were unavailable for 4 patients due to either young age or insufficient clinical documentation. Coarse voice was presented in 11 patients (11/32, 34.37%). Four patients had recurrent pneumonia or asthma (4/32, 12.5%). Developmental delay was detected in 8 patients. In addition to these cases, there was a second syndrome in one case that could explain the developmental delay. The clinical and molecular data of the 32 patients from 25 unrelated families were summarized in Tables S1–S3. Selected case photographs are presented in Figure 2.

3.1 | Genetic Results of Patients

A total of 21 different variants from 25 unrelated families were identified: 11 *EDA* variants (11/21, 52.3%), 7 *EDAR* variants (7/21, 33.3%), 3 *WNT10A* variants (3/21, 14.2%). Seven variants were novel: 5 novel *EDA* variants and 2 novel *EDAR* variants. *EDARADD* gene variants were not detected in our cases.

3.1.1 | *EDA* Gene Variants

The *EDA* gene is located on the X chromosome, and pathogenic variants in this gene exhibit X-linked inheritance. The 11 different *EDA* (NM_001399.5) variants were identified in 14 patients from 11 unrelated families: 6 previously reported and 5 novel (c.1003A>T, c.344C>T, c.785T>G, c.1069dupC, c.334A>T). The cases consisted of 3 heterozygous females and 11 hemizygous males. All *EDA* families had different variants from each other. 6 missense, 3 in-frame deletions, 1 one base pair frameshift duplication, and 1 stop codon variant were detected (Table S1). The detected variants were in different exons: 4 in exon 4, 2 in exon 1, 2 in exon 8, 1 in exon 2, 1 in exon 6, and 1 in exon 7. All variants affected extracellular proteins. Variant-domain relationships were schematized in Figure 3. The clinical and molecular data of the *EDA* patients were summarized in Table S1.

3.1.2 | *EDAR* Gene Variants

EDAR gene related HED is typically inherited in autosomal recessive and autosomal dominant inheritance patterns. The 7 different *EDAR* (NM_022336.4) variants were identified in 11 patients from 8 unrelated families: 5 previously reported and 2 novel (c.586_588del, c.1198C>T). The individual with the c.1198C>T variant was compound heterozygous; the other variant was reported previously. The cases consisted of 3 compound heterozygous, 1 heterozygous, and 7 homozygous variants. The most frequently detected variant was c.71C>A in 3 families, followed by c.442T>C in 2 families. 5 missense, 1 in-frame deletion, and 1 one base pair frameshift deletion variants were detected (Table S2). The different detected variants were in diverse exons: 3 in exon 3, 1 in exon 4, 1 in exon 5, 1 in exon 7, and 1 in exon 12. Variant-domain relationships were schematized in Figure 3. The clinical and molecular data of the *EDAR* patients were summarized in Table S2.

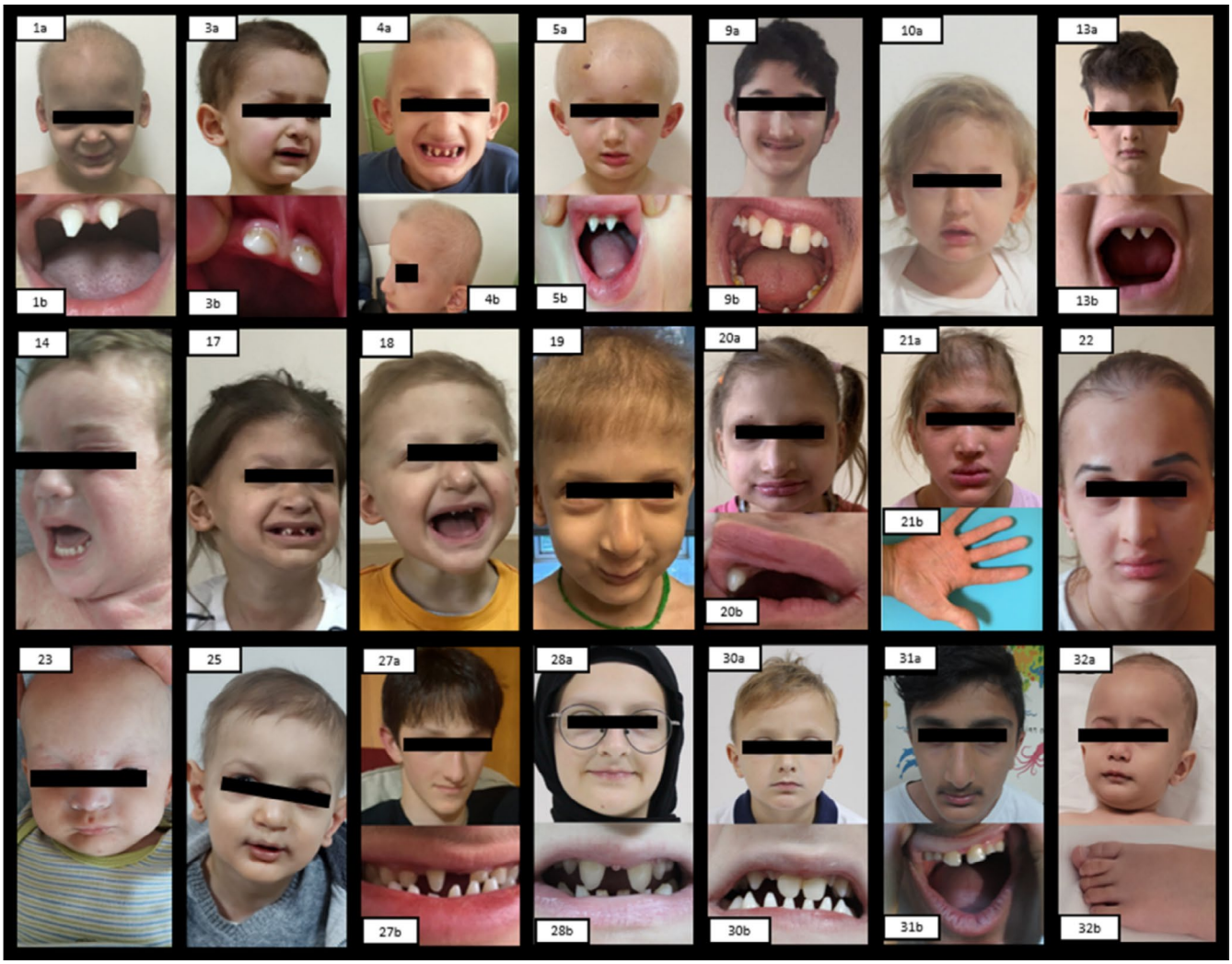

FIGURE 2 | Clinical features of HED patients. Case numbers are indicated on the images. Cases 1, 3, 4, 5, 9, 10, 13, 14 have EDA gene variant; 17, 18, 19, 20, 21, 22, 23, 25 have EDAR gene variant; 27, 28, 30, 31, 32 have WNT10A gene variant. [Colour figure can be viewed at wileyonlinelibrary.com]

3.1.3 | *WNT10A* Gene Variants

Although *WNT10A*-associated HED is usually autosomal recessive, heterozygotes can show partial symptoms like tooth agenesis, reflecting reduced penetrance. The 3 different *WNT10A* (NM_025216.3) variants were identified in 7 patients from 6 unrelated families. The cases consisted of 1 heterozygous and 5 homozygous variants. The most frequently detected variant was c.433G>A in 3 families. 2 different missense and 7 base pairs frameshift duplication variants were detected (Table S3). The different detected variants were in diverse exons: 1 in exon 1, 1 in exon 2, and 1 in exon 3. The clinical and molecular data of the *WNT10A* patients were summarized in Table S3.

4 | Discussion

This study presents the largest known cohort of molecularly diagnosed hypohidrotic ectodermal dysplasia (HED) patients from Türkiye, comprising 32 individuals from 25 unrelated families, with detailed clinical and genetic evaluations focusing on *EDA*, *EDAR*, and *WNT10A* variants. The case series consisted of 44% *EDA* (11/25), 32% *EDAR* (8/25), and 24% *WNT10A* (6/25) families. No *EDARADD* families were identified. The *EDA* gene was the most contributing gene in our cohort (14/32, 43.75%). The *EDA* gene was followed by the *EDAR* (11/32) and *WNT10A* (7/32) genes with 34.37% and 21.87%, respectively. We present seven novel variants in 21 different variants. A total of 11 of 21 different variants were detected in *EDA* (50%), 7 in *EDAR* (31.81%), and 3 in *WNT10A* (18.18%) genes. 5 novel variants were described in EDA, 2 in the *EDAR* genes.

According to HGMD, the proportion of HED attributed to pathogenic variants in the *EDA*, *EDAR*, *EDARADD*, and *WNT10A* genes contributed ~50%–60%, ~10%–15%, ~2%–3%, and 15%–20%, respectively [1, 14]. Cohort studies in the literature reported *EDA* gene variant rates of 41%–87%, *EDAR* gene 4%–20%, *EDARADD* 1.5%–9.8%, and *WNT10A* 0%–25% [3, 16–19]. Our study differed from these cohort studies by having a higher *EDAR* gene variant rate. The higher frequency of *EDAR* variants in our cohort compared to previous studies may be attributed to the relatively high rate of consanguineous marriages in the

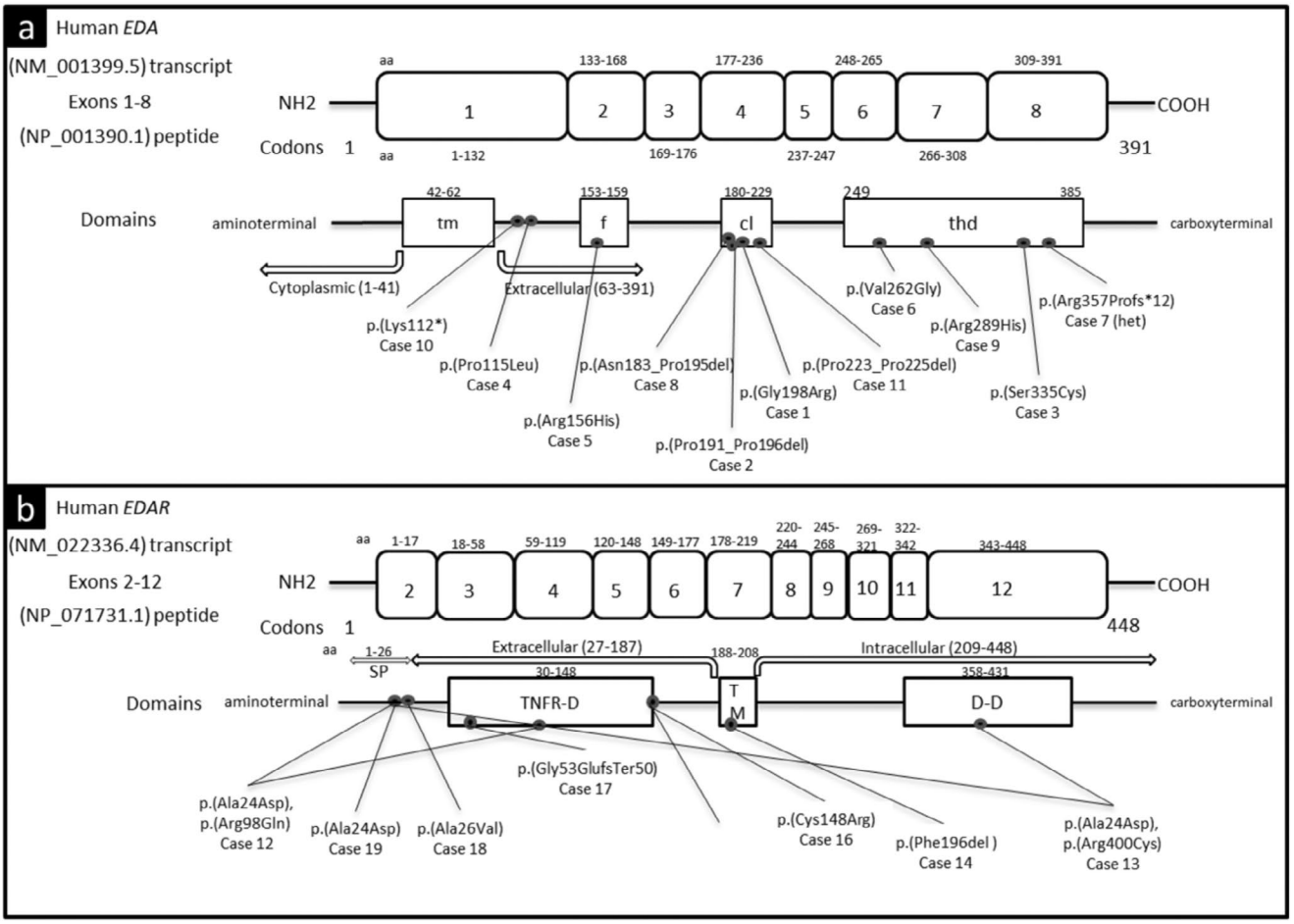

FIGURE 3 | Domains and variants of EDA and EDAR gene. (a) aa, Amino acid; tm, Transmembrane; f, Furin cleavage site; cl, Collagen-like domain; thd, TNF homology domain (UniProtKB/Q92838). (b) aa, Amino acid; TM, Transmembrane; D-D, Death domain; TNFR, Tumor necrosis factor receptor domain (UniProtKB/Q9UNE0).

population we studied, which is known to increase the detection of autosomal recessive conditions. Additionally, differences in ethnic and genetic backgrounds between populations may also contribute to the observed variation in *EDAR* variant frequency.

To the best of our knowledge, our study was the largest cohort from Turkiye to investigate *EDA*, *EDAR*, *EDARADD*, and *WNT10A* genes in HED. Güven Y. et al. previously reported the first cohort study in 17 families from Türkiye: 6 *EDA* (35.29%), 6 *EDAR* (35.29%), 1 *EDARADD* (5.88%), and 4 *WNT10A* (23.52%). This study revealed a lower *EDA* and higher *EDAR* variant rate than other cohorts [20]. Our study combined a larger number of patients; no *EDARADD* cases were detected. The higher rates of *EDA* and *EDAR* cases were manifested. The rate of cases with *WNT10A* and consanguinity of parents was similar. Although some common variants were detected in both studies, the majority of the variants were different in our study. Such discrepancies may be due to ethnic diversity, different cohort sizes, and rates of consanguineous marriage in populations.

A total of 11 different variants were detected in the *EDA* gene, five of which were novel. The novel variants were located in exons 1, 6, and 8. While the classical triad was observed in 4 of the male cases with novel variants (Cases 4–5, 6, 10, 13), a milder phenotype was detected in case 9 (c.785T>G, in exon 6). There is no clear genotype–phenotype correlation described in the literature. However, missense variants, and particularly variants affecting the tumor necrosis factor domain, have been reported in *EDA* gene-associated isolated hypodontia cases [21]. Although the missense variant identified in Case 9 affected the same domain, it was compatible with clinical X-linked HED. A clear genotype–phenotype correlation could not be established. Similarly, no genotype–phenotype correlation could be established between missense variants and variants resulting in frameshift or stop codons.

In our cohort, three female patients were identified as heterozygous carriers of *EDA* variants. Although *EDA*-related HED typically follows an X-linked recessive inheritance pattern and predominantly affects males, heterozygous female carriers may also manifest clinical features to varying degrees. This variability is often attributed to skewed X-chromosome inactivation. In our cases, the three heterozygous females exhibited mild to moderate symptoms, such as hypodontia, sparse scalp hair, and dry skin. These findings align with previous reports indicating that a subset of carrier females can exhibit partial HED phenotypes, although they are generally milder than in hemizygous males [5, 17, 22]. Recognition of this variability is clinically important for appropriate genetic counseling and family screening strategies.

Interestingly, the most prominent finding in Case 14 was severe atopic dermatitis, without any abnormality in sweating and dental development. The identified variant in this case has been previously reported in ClinVar (ClinVar Variation ID: 2716467) with the HED phenotype. However, no detailed clinical information about the associated patient was available. Although atopic dermatitis has been associated with EDA-related HED in previous reports, it has not been described as the predominant clinical feature. The presentation of severe atopic dermatitis as the leading symptom in our case suggests potential phenotypic variability within the spectrum of HED.

Seven different variants in the *EDAR* gene were detected in 11 cases. Two novel variants (c.1198C>T, c.586_588del) were described in our *EDAR* cohort. ten patients have the classical triad of HED. Since case 23 was 4 months old, she could not be evaluated for the classical triad. Case 16 was found to carry a heterozygous variant in the EDAR gene. Nevertheless, the individual exhibited only mild clinical manifestations, consistent with previous studies suggesting that heterozygous EDAR variants may lead to attenuated phenotypes [1, 17]. Neurodevelopmental delay is not a typical feature of ectodermal dysplasia and is not expected in association with EDA, EDAR, or WNT10A variants. However, in our cohort, developmental delay was observed in the EDAR variant group, specifically in eight patients (cases 15, 17–22, and 25). Since most of these patients were consanguineous and whole exome sequencing (WES) was not performed, other potential causes of neurodevelopmental delay could not be excluded. Dual genetic diagnosis was present in 2 of these cases (Cases; 19, 21). Case 19 also had a homozygous pathogenic variant (NM_000179.3, c.3261del) in the *MSH6* gene (*OMIM* *600678). *MSH6* is associated with 'Endometrial cancer, familial', 'Lynch syndrome 5' and 'Mismatch repair cancer syndrome 3' phenotypes. The patient exhibited hyperpigmented macules. While these features are not typically associated with HED, they may reflect the underlying 'Mismatch repair cancer syndrome 3', which is caused by biallelic pathogenic variants in the *MSH6* gene. Therefore, the phenotypic findings in this case likely represent the co-occurrence of two genetically independent conditions. Case 21 had compound heterozygous variants (NM_000083, c.830G>A, c.1580T>C) in the *CLCN1* gene (*OMIM* *118425), besides the *EDAR* gene variant. Biallelic pathogenic variants in the *CLCN1* gene is caused 'Myotonia congenita, recessive' phenotype. Clinical findings such as myotonia, muscle hypertrophy, and stiffness are consistent with autosomal recessive myotonia congenita (Becker type; OMIM #255700). These symptoms are not part of the typical HED spectrum and are considered coincidental but genetically confirmed dual diagnoses. Such dual molecular diagnoses emphasize the importance of careful phenotypic evaluation and broad genetic testing strategies in complex cases.

Cases 21 and 22 also had hypoplastic breast tissue. Palmoplantar hyperkeratosis was observed in cases 20–22. Although the c.442T>C variant in the *EDAR* gene has been reported in the literature before, it was associated with hypoplastic breast tissue in our cases for the first time [23]. Although the genotype–phenotype correlation has not been fully defined, it has been reported in the literature that heterozygous variants are associated with milder phenotypes, and some variants are presented with hypoplastic breast tissue and palmoplantar hyperkeratosis [23–25].

Three different variants were identified in *WNT10A*. The most common variant was c.433G>A, as previously reported by Güven Y. et al. [20]. Interestingly, hyperhidrosis was detected in case 27 with the c.99_105dup variant, while hypohidrosis was detected in another case with the same variant in cases 29–30. Although hypohidrosis is a hallmark feature of HED, hyperhidrosis has also been reported in patients with WNT10A-related HED in the literature, indicating phenotypic variability within this subgroup [1, 26]. A milder phenotype, nail agenesis in the left foot and microdontia in canines without oligodontia, was detected in case 32 with the heterozygous c.311G>A variant. The homozygous c.311G>A variant was previously reported in 3 sibs with oligodontia [27]. This was consistent with the mild phenotype reported in heterozygous cases in the literature [18]. These findings are consistent with the growing body of evidence suggesting that heterozygous WNT10A variants can result in mild phenotypic features, particularly isolated dental anomalies. Although WNT10A-related ectodermal dysplasia is classically inherited in an autosomal recessive manner, monoallelic variants have been associated with incomplete penetrance and variable expressivity, especially in the context of non-syndromic tooth agenesis [17, 28]. Therefore, the observation in Case 32 supports the notion that heterozygous carriers may manifest partial features of ectodermal dysplasia, even in the absence of a second pathogenic allele. The microdontia of canines has rarely been reported in male heterozygous cases in the literature [28]. *WNT10A* pathogenic variants may be associated with a wide spectrum of disorders ranging from isolated oligodontia to disruption of all other ectodermal derivatives [18].

5 | Limitations and Future Directions

Despite the broad scope of our findings, the absence of EDARADD variants and the relatively small sample size limit the generalizability of our conclusions. Increasing the cohort size and adding functional studies of novel variants will improve our understanding of the EDA/NF-κB and WNT/β-catenin pathways. Additionally, collaborative studies across diverse populations are important to clarify the full genetic and phenotypic spectrum of HED. Further research is needed to explore the wider implications of these mutations and to refine genotype–phenotype correlations for better therapeutic approaches.

6 | Conclusions

This study provides a detailed clinical and molecular characterization of 32 HED patients from 25 unrelated families in Türkiye. We identified seven novel variants: five in the *EDA* gene and two in the *EDAR* gene, broadening the known variant spectrum of HED. The majority of cases harbored variants in *EDA* and *EDAR*, while no *EDARADD* variants were detected. Notably, we observed atypical presentation in the *EDA* gene with atopic dermatitis. It is also essential for clinicians to consider the ectodermal dysplasia disease group in patients presenting with severe atopic dermatitis to facilitate accurate diagnosis and comprehensive care. In several cases, dual molecular diagnoses provided

insight into co-occurring phenotypes. Additionally, dual molecular diagnoses in several individuals provided insight into coexisting genetic conditions. These results expand the known mutational spectrum of HED and contribute to understanding genotype–phenotype correlations. Our findings underscore the importance of integrating genetic testing into clinical evaluation and highlight the utility of genetic counseling in managing affected families and planning reproductive strategies.

Author Contributions

Z.E. performed and interpreted the genetic tests, wrote the manuscript, and collected data. Other authors provided support for case consultations, data collection, and article writing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.70030.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.