Genetic Findings in a Cohort of 250 Patients with Clinical Suspicion of Ectodermal Dysplasia

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Introduction

Ectodermal dysplasias (ED) are a group of heterogeneous conditions that affect the hair, teeth, sweat glands and nails. ED may result in life-threatening hyperthermia, recurrent respiratory infections, abnormal function of orofacial structures and chronic skin concerns. The most common form of ED is X-linked hypohidrotic. The molecular findings within an unselected referral population receiving genetic testing for the indication of ED have not been characterized. We assessed the utility of next-generation sequencing (NGS)-based multi-gene panels for individuals with suspected ED and provide an overview of the positive genetic findings.

Methods

A retrospective review of molecular results for 252 patients referred for genetic testing with a clinical suspicion of ED was performed. Panel testing included both sequence and copy number variant (CNV) analyses of NGS data. The target region included the coding exons (+/- 20 bp from the intron/exon boundary) in addition to noncoding variants (>10 base pairs from the intron/exon boundary) catalogued as disease-associated in ClinVar and the Human Gene Mutation Database (HGMD). Variant interpretation and reporting were performed using modified ACMG/AMP guidelines. A positive result was defined as the identification of pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the patient's reported phenotype and associated disease inheritance. Clinical information was provided by the referring health care provider on the test requisition form.

Results

In this cohort, 54.0% of patients (136/252) were female and the median patient age at time of testing was 9 years (range, 1 month to 75 years) (Table 1). A positive result was reported in 45.2% of patients (114/252).

LP/P variants were identified in 15 genes; the most frequently involved genes were *EDA* (44.7%, n=51), associated with X-linked hypohidrotic ED, and *WNT10A* (29.8%, n=34). Other genes contributing to a positive result, in decreasing frequency, were *TP63, GJB6, EDAR, LRP6, GJB2, PORCN, DLX3, DSP, HR, LIPH, PAX9*, *IKBKG,* and *RMRP* (Figure).

Interestingly, one patient was found to be mosaic for a variant in *EDA* (allele fraction 25%).

Of positive results, CNVs were the causative variant in 4.4% (5/114) of cases. One patient (0.9%) had a 4-exon deletion of *IKBKG* and four patients (3.5%) had CNVs that were ≤1 exon in size in *EDA*.

Further, 2.6% (3/114) of positive reports were explained by noncoding variants involving the *EDA*, *HR*, and *RMRP* genes.

Finally, 5.2% (13/252) of patients with inconclusive results had a suspicious VUS that had the potential to be reclassified to likely pathogenic with family member testing.

For patients with ectodermal dysplasia, 7% (8/114) of positive results were due to:

Small (≤4 exons in size) deletions

(n=5)

Disease-causing deep intronic and regulatory variants

(n=3)

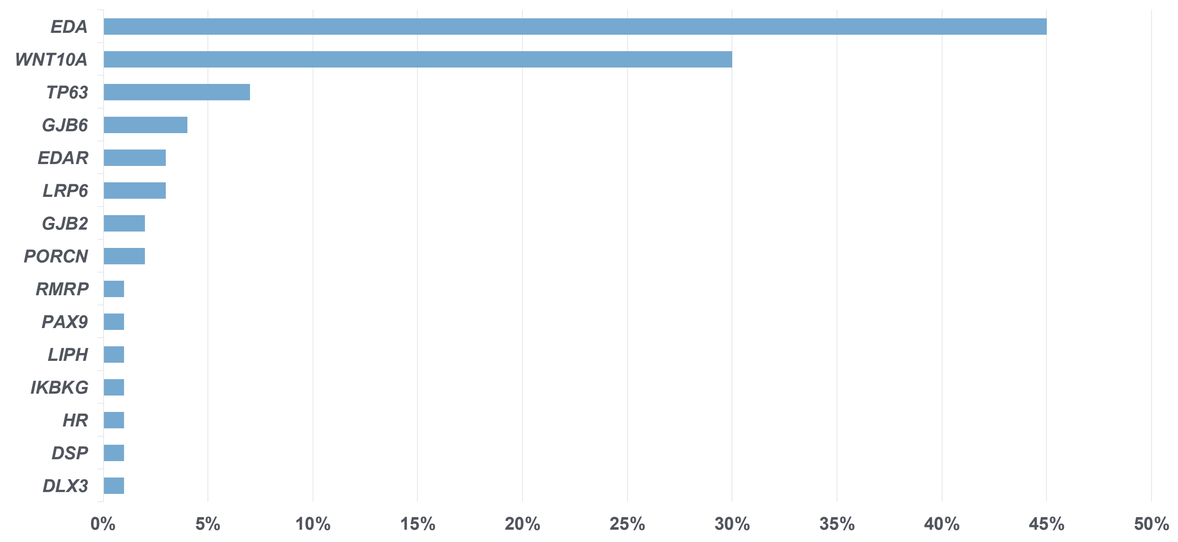

Figure. Frequency of positive results by gene

Table 1. Cohort demographics and positive rate per demographic category.

Category	Number in total cohort	% of total cohort (n=252)	Number in positive cohort	% of positive cohort (n=114)	Positive rate by category
Sex					
Male	116	46.0%	57	50%	49.1% (57/116)
Female	136	54.0%	57	50%	41.9% (57/136)
Age range at testing					
0-10 years	128	50.8%	54	47.4%	42.2% (54/128)
11-18 years	54	21.4%	20	17.5%	37.0% (20/54)
19-40 years	54	21.4%	32	28.1%	59.3% (32/54)
41-75 years	16	6.3%	8	7.0%	50.0% (8/16)

Table 2. Clinical presentation by cohort.

Hair, teeth, nails and sweat glands affected?	Positive	Suspicious VUS	Inconclusive
4 of 4 affected	5	1	5
3 of 4 affected	30	4	38
2 of 4 affected	35	7	42
1 of 4 affected	24	1	29
Not specified	20	0	11

Conclusions

- Half of all patients tested with NGS-based panels for the indication of ED had a positive result (45.2%) or a potentially positive (5.2%) result.
- While 3 genes accounted for the majority of positive results (82%), 12 genes on this panel accounted for the remaining 18%, demonstrating the clinical utility of a multigene panel.
- A comprehensive testing approach including noncoding variants and the ability to detect small CNVs increased the positive rate in this cohort (8/114, 7%).
- The positive and inconclusive cohorts did not differ significantly in their clinical presentations suggesting the need to offer genetic testing broadly in this patient population.

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Conflict of interest statement: All authors are employed by Blueprint Genetics.

References:

1. Deshmukh S, Prashanth S. Ectodermal dysplasia: a genetic review. *Int J Clin Pediatr Dent.* 2012;5(3):197-202.
2. Wright JT, Grange DK, Fete M. Hypohidrotic Ectodermal Dysplasia. 2003 Apr 28 [Updated 2022 Oct 27]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1112/