

EDA1 Gene Testing in Hypo-/Anhidrotic Ectodermal Dysplasia

DISORDER ALSO KNOWN AS

HED; Anhidrotic ectodermal dysplasia; Christ-Siemens-Touraine Syndrome

CLINICAL FEATURES

Affected males have hypotrichosis with fine, sparse and light-colored scalp and body hair. Beard hair is often normal. Other features include a decreased ability to sweat, which often leads to severe heat intolerance, hypodontia and conical or peg shaped teeth. The facial features are characterized by dark pigmented skin around the eyes, saddle nose and full lips. The function of lacrimal, meibomian and other glands is defective and there is thick nasal secretion and cerumen. Absent or accessory nipples are not uncommon. Female carriers of this disorder may have some minor symptoms, including thin hair, patches of hypohidrosis, and abnormal dentition.

GENETICS

Hypo-/Anhidrotic Ectodermal Dysplasia has an X-linked recessive inheritance pattern, although female carriers may have clinical symptoms. New pathogenic variants account for some affected males where the mother cannot be shown to carry a variant.

TEST METHODS

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice sites of the EDA1 gene (exons 1, 3-9) is analyzed. In females, concurrent targeted array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of this gene. If a sequence change or deletion is identified, it is confirmed by a second analysis, using sequence, heteroduplex or restriction fragment analysis, quantitative PCR or another appropriate method.

TEST SENSITIVITY

EDA1 gene variants have been found in 75% to 95% of familial hypo-/anhidrotic ectodermal dysplasia and about 50% of sporadic cases. Sequencing can detect about 95% of EDA1 variants in males. Sequence analysis is less sensitive in females because partial or whole gene deletions would be missed. However, the inclusion of array-based exon-level deletion/duplication analysis (ExonArrayDx) increases the sensitivity to about 95% for females as well.

VARIANT SPECTRUM

Most variants reported to date in the EDA1 gene associated with HED are missense variants, although some nonsense variants and deletions/insertions have been described. They usually cluster in 3 functional domains of ectodysplasin. A variant hotspot involves the Arginine codons 155 and 156 in the furin subdomain. Large deletions of one or more exons or of the entire EDA1 gene have been reported in approximately 10% of patients, and rarely intragenic duplications may also be found.

REFERENCES:

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2. Vincent et al. 2001 Eur J Hum Genet 9:355-363
3. Paakkonen et al. 2001 Hum Mut 17:349
4. Al et al. 2014 Br J Dermatol 171(3):671-673