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Prevalence and Patient Characteristics of Ectodermal Dysplasias in Denmark

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IMPORTANCE Ectodermal dysplasias constitute a group of rare genetic disorders of the skin and skin appendages with hypodontia, hypotrichosis, and hypohidrosis as cardinal features. There is a lack of population-based research into the epidemiology of ectodermal dysplasias.

OBJECTIVE To establish a validated population-based cohort of patients with ectodermal dysplasia in Denmark and to assess the disease prevalence and patient characteristics.

DESIGN, SETTING, AND PARTICIPANTS This nationwide cohort study used individual-level registry data recorded across the Danish universal health care system to identify patients with ectodermal dysplasias from January 1, 1995, to August 25, 2021. A 3-level search of the Danish National Patient Registry and the Danish National Child Odontology Registry was conducted to identify patients with diagnosis codes indicative of ectodermal dysplasias; patients registered in the Danish RAREDIS Database, the Danish Database of Genodermatoses, and local databases were also added. The search results underwent diagnosis validation and review of clinical data using medical records. Of 844 patient records suggestive of ectodermal dysplasias, 791 patients (93.7%) had medical records available for review. Positive predictive values of the diagnosis coding were computed, birth prevalence was estimated, and patient characteristics were identified. Data analysis was performed from May 4 to December 22, 2023.

RESULTS The identified and validated study cohort included 396 patients (median [IQR] age at diagnosis, 13 [4-30] years, 246 females [62.1%]), of whom 319 had confirmed ectodermal dysplasias and 77 were likely cases. The combined positive predictive value (PPV) for ectodermal dysplasia–specific diagnosis codes was 67.0% (95% CI, 62.7%-71.0%). From 1995 to 2011, the estimated minimum birth prevalence per 100 000 live births was 14.5 (95% CI, 12.2-16.7) for all ectodermal dysplasias and 2.8 (95% CI, 1.8-3.8) for X-linked hypohidrotic ectodermal dysplasias. A molecular genetic diagnosis was available for 241 patients (61%), including *EDA* (n = 100), *IKBKG* (n = 55), *WNT10A* (n = 21), *TRPS1* (n = 18), *EDAR* (n = 10), *P63* (n = 9), *GJB6* (n = 9), *PORCN* (n = 7), and other rare genetic variants.

CONCLUSIONS AND RELEVANCE The findings of this nationwide cohort study indicate that the prevalence of ectodermal dysplasias was lower than previously reported. Furthermore, PPVs of the search algorithms emphasized the importance of diagnosis validation. The establishment of a large nationwide cohort of patients with ectodermal dysplasias, including detailed clinical and molecular data, is a unique resource for future research in ectodermal dysplasias.

Supplemental content

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Ectodermal dysplasias (EDs) are a heterogeneous group of genetic disorders affecting the ectodermally derived tissues, typically involving the skin and appendages (eg, hair, teeth, nails, and eccrine sweat glands).[1] Cardinal features of EDs include hypohidrosis, hypotrichosis, nail dystrophy, and hypodontia.[1] In the original clinical classification by Newton Freire-Maia, EDs were divided into 15 subgroups based on different combinations of the 4 cardinal features or other ectodermal derivates involved.[2] Historically, more than 180 different EDs have been described based on clinical presentation. However, increasing insights into the genetic background of EDs have prompted changes to classification systems based on the disease-related genes and molecular pathways.[1,3-5] In 2017, an international working group consolidated the EDs to approximately 100 entities,[1] and in 2022, the most recent consensus group updated that number to 49 entities.[3]

To our knowledge, there are no published nationwide population-based studies of the entire group of EDs, and there are few and diverging reports on ED occurrence, primarily from small studies without denominators and restricted to specific ED subtypes. Previous studies have reported prevalence estimates of 10 to 70 cases per 100 000 births.[6-8] A Danish registry-based study on X-linked hypohidrotic ED (XLHED) reported a prevalence of 4.2 cases per 100 000 based on molecularly confirmed and clinically diagnosed cases, and 21.9 per 100 000 when including a feature-based search; however, these cases were not validated.[9]

Given that EDs have been associated with impaired quality of life[10,11] and increased mortality and morbidity,[12-15] studies of the occurrence, presentation, and prognosis of EDs are important for improving the management of care and outcomes for these patients. Our objectives were to use the Danish health registries to establish a validated nationwide cohort of patients with ED and to assess ED prevalence and patient characteristics.

Key Points

Question What is the ectodermal dysplasias prevalence in Denmark and what are the patient characteristics?

Findings This nationwide population-based cohort study used Danish registries to identify and characterize 396 validated cases of ectodermal dysplasia, showing a minimum birth prevalence of 14.5 cases per 100 000 live births for all ectodermal dysplasias and 2.8 cases for X-linked hypohidrotic ectodermal dysplasia.

Meaning The findings of this nationwide cohort study indicate that the prevalence of ectodermal dysplasia was lower than previously reported, and the detailed clinical and molecular data provide a unique resource for future ectodermal research.

Methods

This nationwide population-based cohort study was approved by the Danish Data Protection Agency (No. 1-16-02-143-21). Central Denmark Region waived informed consent and granted access to medical records data (No. 1-45-70-76-21) in accordance with The Danish Health Care Act. We applied the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Setting and Data Sources

Denmark has a universal health care system with free access to tax-financed health care for all residents (approximately 5.8 million inhabitants).[16] Routinely collected health data are recorded in nationwide registries using a unique personal identifier that allows for accurate registry linkage in studies with all Danish residents as the source population.[17,18]

We used linked data from the Danish National Patient Registry (DNPR), the National Child Odontology Registry (SCOR), the Danish National Database of Rare Genetic Diseases (RAREDIS), and the Danish Genodermatosis Database (DGD). The DNPR contains hospital admission records from 1977 to present, and outpatient visits from 1994 to present at all of the hospitals in Denmark. These records include the diagnoses registered by the treating physician per the *International Classification of Diseases, Eighth Revision* (in use until 1994), and the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* thereafter.[19] The SCOR is a nationwide odontological registry containing childhood dental care information from municipal dental clinics (1972 to present).[20] RAREDIS is a national clinical database with clinical and genetic data regarding patients with rare diseases; data have been submitted by treating clinicians since 2007. The DGD is a research database containing data from 5 dermatology departments in Denmark from 2014 to the present; it includes clinical and diagnostic information as well as family-case linkage for patients with genodermatoses.

Cohort Identification

We searched the DNPR and SCOR for patients whose records were suggestive of ED from January 1, 1995, to August 25, 2021, using 3 search algorithms (detailed in eTable 1 in Supplement 1). In order of priority, the algorithms searched for patient records that contained (1) specific *ICD-10* codes for various ED disorders; (2) 2 or more cardinal ED features in different tissues (hypotrichosis, hypodontia, hypohidrosis, nail dystrophy); or (3) 1 cardinal ED feature and 2 or more minor features. To ensure feasibility, we included algorithm 3 as a sensitivity analysis restricted to only Aarhus University Hospital contacts (visits).

We chose the diagnosis codes by searching the Danish version of the *ICD-10* (SKS-browser, version 4.05[21]), including historical codes. In a subanalysis assessing how changing ED classifications affect ED prevalence, we included specific *ICD-10* codes for entities previously considered to be EDs, eg, monilethrix (eTable 1 in Supplement 1). To improve completeness, we also searched RAREDIS and DGD for various ED-related codes from the *ICD-10*, OMIM (Online Mendelian Inheritance in Man), and ORPHAcodes (Orphanet rare disease nomenclature) (eTable 2 in Supplement 1).

One author (L.K.H.) reviewed the patients' medical records for validation and detailed patient characterization. Data on patient and family medical history, phenotypical features,

patient treatment course and care management, and genetic test results were extracted to a piloted REDCap form[22,23] (eTable 3 in Supplement 1) to the extent available. Local databases and family records linked to the identified patients were assessed when available.

We validated cases using the 2022 definition from the International ED Consensus Group.[3] Thus, patients with specific ED-like phenotypes classified elsewhere (eg, monilethrix) were excluded.[1,3] When uncertain, case validation was determined by consensus agreement among 3 authors (L.K.H., K.R., and M.S.). We included patients based on 2 levels of certainty: confirmed or likely ED. Among likely cases, we included those clinically suggestive of ED but without firm clinical and/or genetic diagnoses and those with a pathogenic gene variant of an ED-associated gene and description of only 1 affected ectodermal derivate if the medical record did not clearly state that other ectodermal derivates were unaffected. We excluded cases that did not fulfill the applied ED definition, including patients with gene variations without ED-related manifestations (including unaffected female carriers of XLHED).

Statistical Analyses

We computed descriptive statistics for the entire cohort and ED subgroups. As an estimate of the validity for the overall sample, for the 3 search algorithms, and for each ED-specific diagnosis code, we computed the positive predictive values (PPVs) with 95% CIs as the number of patients with a confirmed or likely ED diagnosis after validation, divided by those identified by the search. We excluded patients whose medical records were unavailable. We estimated the sensitivity of the DNPR search algorithm 1 based on the number of additional validated patients from our other searches.

We estimated the minimum birth prevalence of ED with 95% CIs for annual birth cohorts and from 1995 to 2011 and 1995 to 2001 for a minimum follow-up for a first-time diagnosis recorded before age 10 and 20 years, respectively. We estimated prevalence proportions using annual live births reported by Statistics Denmark as denominators.[24] We performed a sensitivity analysis including patients with missing records born from 1995 to 2011.

We defined the diagnosis date as the date of the patient's ED-defining contact (visit) registered with any of the listed ED-specific *ICD-10* codes or for algorithms 2 and 3 when the second or third code was fulfilled, respectively (eTable 1 in Supplement 1). Statistical testing was not used given the descriptive nature of the study. Data analyses were performed from May 4 to December 22, 2023, using Stata, version 17.0 (StataCorp LLC).

Results

Patient Identification

The database searches identified 844 patients records suggestive of ED, including 787 patients identified by the 3 DNPR-based algorithms (algorithm 3 restricted to Aarhus University Hospital). The numbers of patients uniquely identified from these prioritized searches (populations 1, 2, and 3) were 530, 147, and 110 patients, respectively. The remaining 57 patients were identified from the additional data sources referenced in the Methods (eFigure 1 in Supplement 1 shows the overlap among the different searches). Despite substantial overlap between DGD and RAREDIS using algorithm 1, an additional 26 patients were identified from RAREDIS and an additional 5 from the DGD.

Diagnosis Validation

Figure 1 depicts the validation process. We were able to retrieve medical records for 791 of 844 patients (validation rate, 93.7%). Patients who were excluded due to missing records had been diagnosed in earlier calendar years and had a median (IQR) age of 22 (10-43) years compared with 15 (7-27) years for those with complete medical records available.

Validated ED Cohort

The final validated ED cohort comprised 396 patients (median [IQR] age at diagnosis, 13 [4-30] years; 246 females [62.1%] and 150 males [37.9%]), of whom 319 had confirmed ED and 77 had likely ED. The latter group included patients with a genetic variant suggestive of ED plus involvement of 1 ectoderm derivate noted in their medical records (n = 26), and patients with clinically suggested ED but no definitive clinical and/or genetic diagnosis per the available information (n = 51). Genetic confirmation was available for 241 of 396 patients (61%).

From the 791 patients with available medical records, 395 were excluded: 87 records had coding mistakes (more information follows) and 67 patients had other congenital syndromic disorders (ie, misdiagnosed); 33 had isolated nail dystrophy; 28 had isolated hypotrichosis or alopecia; 91 had isolated tooth agenesis; 17 had been referred on suspicion of ED diagnosis that was rejected after assessment; and the final 90 had other non-ED diagnoses at validation (primarily from populations 2 and 3).

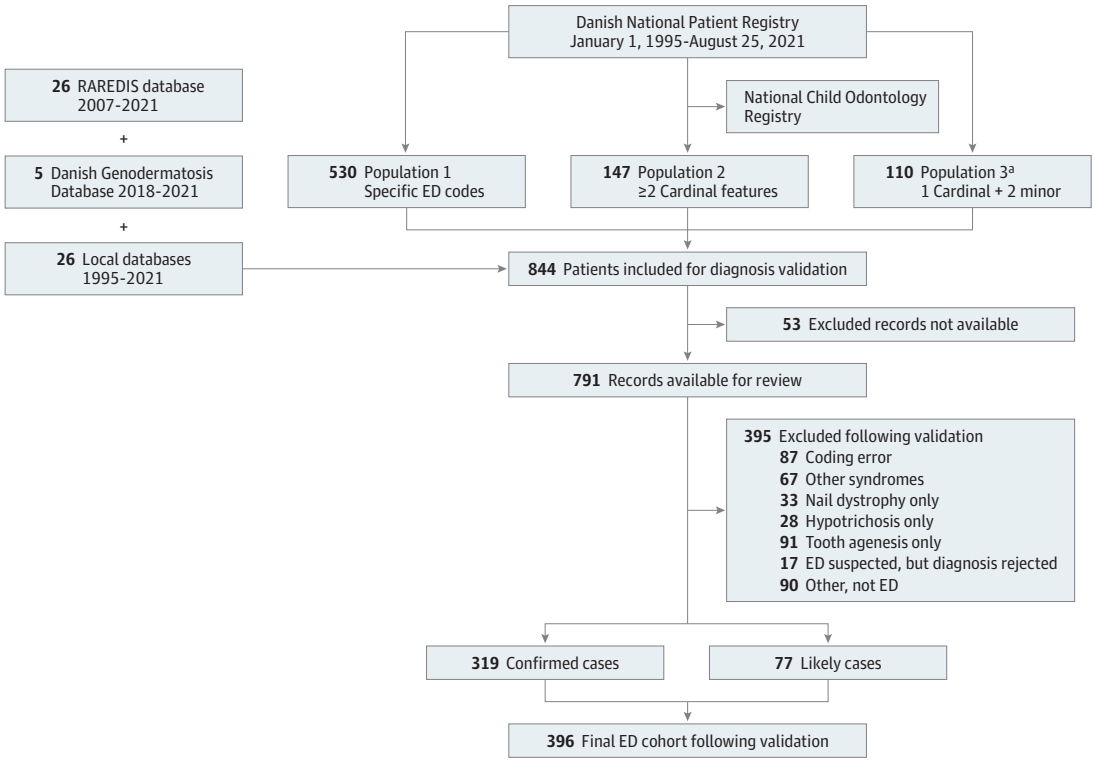
The PPV was 50.1% (95% CI, 46.6%-53.5%) for all data sources combined and 46.6% (95% CI, 43.0%-50.2%) for the DNPR-based searches (**Table 1**). The PPV was 67.0% (95% CI, 62.7%-71.0%) for search algorithm 1, and markedly lower for the feature-based search algorithms. The PPV of search algorithm 1 varied between 62.1% (95% CI, 57.9%-66.1%) and 69.4% (95% CI, 65.4%-73.2%) in a bias analysis including patients with missing medical records. The *ICD-10* codes with the highest PPVs were the specific subcodes of Q82.4 ectodermal dysplasia, with PPVs greater than 90%.

The PPV for Goltz syndrome (Q87.8E) was only 18.2% (95% CI, 9.2%-32.8%) due to frequent coding errors of Gorlin-Goltz syndrome (ie, nevoid basal cell carcinoma syndrome) as Goltz-Gorlin syndrome (ie, focal dermal hypoplasia). We also found other coding mistakes, including errors explained by the resemblance of the *ICD-10* codes for spastic tetraplegia (G82.4) and ectodermal dysplasia (Q82.4). The sensitivity of ED-specific codes in DNPR (algorithm 1) was 329 of 396, or 83.1% (95% CI, 79.1-86.5), using the entire validated cohort as reference.

Birth Prevalence

There was no substantial calendar trend in ED birth prevalence except for a downward tendency in more recent years,

Figure 1. Identification of Patients With Ectodermal Dysplasia (ED) and Diagnosis Validation in Denmark



[a] Only for patients of the Aarhus University Hospital.

RAREDIS is the Danish National Database of Rare Genetic Diseases.

Table 1. Positive Predictive Values of Search Algorithms[a] and Specific *ICD-10* Codes for the Identification of Patients With Ectodermal Dysplasias (ED)

	Cases of ectodermal dysplasia, No.					
			Confirmed or likely cases		Confirmed cases only	
Search algorithm	All	Records available	No.	PPV, % (95% CI)	No.	PPV, % (95% CI)
All searches combined	844	791	396	50.1 (46.6-53.5)	319	40.3 (37.0-43.8)
DNPR searches combined	787	734	342	46.6 (43.0-50.2)	276	37.6 (34.2-41.2)
Algorithm 1–specific *ICD-10* codes	530	491	329	67.0 (62.7-71.0)	272	55.4 (51.0-59.8)
Q82.3 Incontinentia pigmenti	107	97	73	75.3 (65.6-82.9)	68	70.1 (60.2-78.5)
Q82.4 ED (subcodes included)	384	358	256	71.5 (66.6-76.0)	204	57.0 (51.8-62.0)
Q82.4 ED (subcodes excluded)	327	302	209	69.2 (63.7-74.2)	168	55.6 (50.0-61.2)
Q82.4A ED, anhidrotic	43	43	41	95.3 (82.6-98.9)	38	88.4 (74.4-95.2)
Q82.4B ED, hidrotic	49	47	42	89.4 (76.4-95.6)	31	66.0 (51.0-78.3)
Q82.4C ED, hypohidrotic	61	61	59	96.7 (87.5-99.2)	56	91.8 (81.5-96.6)
Q87.8E Goltz syndrome	47	44	8	18.2 (9.2-32.8)	8	18.2 (9.2-32.8)
Algorithm 2[b]	147	134	11	8.2 (4.6-14.3)	3	2.2 (0.7-6.8)
DNPR only	61	59	7	11.9 (5.7-23.2)	3	5.1 (1.6-14.9)
Hypo/oligodontia in SCOR	86	75	4	5.3 (2.0-13.6)	0	
Algorithm 3 (AUH only)[c]	110	109	2	1.8 (0.5-7.1)	1	0.9 (0.1-6.4)
RAREDIS search	67	67	65	97.0 (88.6-99.3)	59	80.1 (77.7-94.0)
DGD search	45	45	43	95.6 (83.3-98.9)	41	91.1 (78.1-96.7)

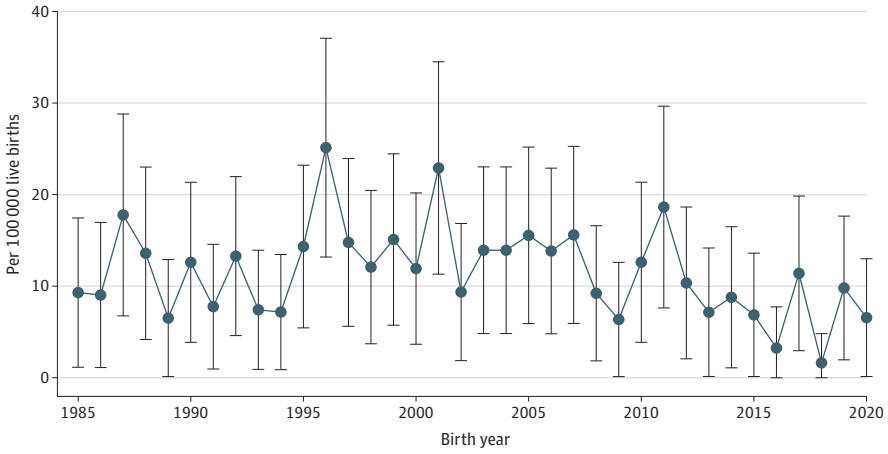
Abbreviations: AUH, Aarhus University Hospital; DGD, Danish Genodermatosis Database; DNPR, Danish National Patient Registry; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; PPV, positive predictive value; RAREDIS, Danish National Database of Rare Genetic Diseases; SCOR, Danish National Child Odontology Registry.

[a] Detailed descriptions of search algorithms are available in eTables 1 and 2 in Supplement 1.

[b] Excluding patients already identified by algorithm 1.

[c] Excluding patients already identified by algorithms 1 and 2.

Figure 2. Annual Prevalence of Ectodermal Dysplasia at Birth in Denmark, 1985 to 2020



Circles represent the birth prevalence estimates (per 100 000 live births) and bars represent 95% CIs.

which had a shorter follow-up time (**Figure 2**). The estimated minimum birth prevalence from 1995 to 2011 (at least 10 years of follow-up to receive a first-time diagnosis) for all ED cases (n = 160) was 14.5 cases per 100 000 live births (95% CI, 12.2-16.7). From 1995 to 2001 with 20 years of follow-up (n = 78), the birth prevalence increased to 16.6 per 100 000 live births (95% CI, 12.9-20.3). In a sensitivity analysis that included all unvalidated (potential) cases in individuals born from 1995 to 2011 (n = 13), the birth prevalence increased from 14.5 to 15.6 cases per 100 000 live births (95% CI, 13.3-18.0). Instead, when including validated cases with diagnoses previously classified as EDs (n = 14; eTable 1 in Supplement 1), the 1995 to 2011 birth prevalence was 15.7 per 100 000 (95% CI, 13.4-18.1).

The birth prevalence of molecularly confirmed XLHED was 2.8 per 100 000 live births (95% CI, 1.8-3.8) for the 1995 to 2011 birth cohorts (n = 31) and 4.5 per 100 000 live births (95% CI, 2.6-6.4) for the 1995 to 2001 birth cohorts (n = 21). These estimates increased to 4.5 per 100 000 live births (95% CI, 3.3-5.8) and 6.6 per 100 000 live births (95% CI, 4.3-8.9), respectively, when including hypohidrotic ED (HED) cases without genetic confirmation.

Patient Characteristics

The patient characteristics of the cohort and selected subgroups are summarized in **Table 2**. Genetic testing had been performed for 292 patients (74%), identifying a genetic diagnosis in 241 patients (61% [83% of those tested]). The median (IQR) age at diagnosis was 13 (4-30) years overall and 5 (1-10) years when restricted to those born during the study period beginning on January 1, 1995. The median (IQR) age at the genetic diagnosis was 8 (6-36) years overall and 7 (2-13) years for patients born after 1995. Of DNPR registrations with diagnosis codes included in the search algorithms, 254 patients (64%) had visited a dental or maxillofacial department; 211 (53%), dermatology; 203 (51%), pediatrics; 108 (27%), otorhinolaryngology; 105 (27%), clinical genetics; 48 (12%), orthopedic surgery; and 46 (12%), ophthalmology.

The most frequently altered gene was *EDA* (n = 100) followed by *IKBKG* (n = 55), *WNT10A* (n = 21), *TRPS1* (n = 18), *EDAR* (n = 10), *TP63* (n = 9), *GJB6* (n = 9), *PORCN* (n = 7), and other rare genetic variants (eFigure 2 in Supplement 1). The cohort also included rare subtypes, such as HED with immunodeficiency, Clouston syndrome, ulnar-mammary syndrome, keratitis-ichthyosis-deafness syndrome, and oculodentodigital dysplasia (eTable 4 in Supplement 1 provides genetic diagnoses according to the 2022 ED classification).

In addition, hypohidrosis or anhidrosis was noted in 135 patients (34%); hypodontia or oligodontia in 293 (74%); nail involvement in 105 (27%); and hair involvement in 235 (59%), most frequently hypotrichosis (42%) and fragile hair (17%) (Table 2). Dry skin (128 [32%]) and dry mouth (48 [12%]) were also reported. Of note, female patients with XLHED had several cardinal features, eg, 20 (40%) had hypohidrosis and 46 (92%) had tooth involvement. Oligodontia was more common among males with XLHED, and females with XLHED generally had fewer missing teeth. A high frequency of craniofacial dysmorphology (148 [37%]) was found in the cohort, particularly midfacial hypoplasia (Table 2).

Discussion

Using Danish health registries to identify and characterize a nationwide cohort of patients with ED, this study provides what is, to our knowledge, the first validated population-based epidemiologic findings of the entire group of EDs. Given the estimated overall ED birth prevalence of 14.5 cases per 100 000 live births, we propose that the true disease prevalence is lower than previously considered. Thus, the estimated birth prevalence in Denmark from 1995 to 2011 was approximately 5 times lower than the frequently cited estimate of 70 cases per 100 000 live births.[6,13] This difference may be partly explained by the new and more stringent definition of EDs, which has reduced the total number of disease subtypes substantially.[3] However, bias analyses, including unvalidated cases as well as previous ED entities, produced results that were still well below previously reported prevalence estimates. Diagnostic delays may affect

Table 2. Reported Characteristics of the Cohort and Selected Subgroups of Patients With Confirmed or Likely Ectodermal Dysplasia

Characteristic	No. (%)								
				Common subgroups					
	All cases	Confirmed cases	Likely cases	Males with XLHED	Females with XLHED	IP	OODD/ SSPS	TRPS	AEC/EEC/ LM/RH syndrome
Total patients	396	319 (81)	77 (19)	50	50	75	21	20	21
Female sex	246 (62)	203 (64)	43 (56)	NA	50	71 (95)	17 (81)	13 (65)	10 (48)
Male sex	150 (38)	116 (36)	34 (44)	50	NA	4 (5)	4 (19)	7 (35)	11 (52)
Age at diagnosis, median (IQR), y	13 (4-30)	13 (3-31)	13 (7-21)	6 (1-24)	30 (12-50)	3 (0-29)	21 (5-38)	15 (8-26)	12 (4-22)
Born during study period (≥1995)	5 (1-10)	3 (0-9)	8 (6-12)	2 (1-2)	8 (5-12)	0 (0-0)	6 (3-11)	13 (4-15)	7 (3-14)
Genetic test (any type)	292 (74)	255 (80)	37 (48)	50 (100)	50 (100)	59 (79)	21 (100)	19 (95)	12 (57)
Genetic diagnosis	241 (61)	215 (67)	26 (34)	50 (100)	50 (100)	54 (72)	21 (100)	18 (90)	9 (43)
Genetic department visit	105 (27)	90 (28)	15 (19)	13 (26)	19 (38)	26 (35)	12 (57)	5 (25)	3 (14)
Age at genetic diagnosis, median (IQR), y	18 (6-36)	17 (6-32)	22 (9-49)	9 (2-35)	30 (17-49)	18 (1-31)	24 (13-43)	15 (8-26)	15 (8-21)
Positive family history	251 (63)	214 (67)	37 (48)	38 (76)	44 (88)	40 (53)	16 (76)	15 (75)	11 (52)
Sweat gland involvement	135 (34)	132 (41)	3 (4)	45 (90)	20 (40)	<3	8 (38)	0	3 (14)
Hypohidrosis	123 (31)	120 (38)	3 (4)	38 (76)	20 (40)	<3	7 (35)	0	3 (14)
Anhidrosis	12 (3)	12 (4)	0	8 (16)	0	0	0	0	0
Heat intolerance	74 (19)[a]	74 (23)	<3	26 (52)	9 (18)	0	4 (19)	0	<3
Scalp hair involvement	235 (59)	218 (68)	17 (22)	42 (84)	25 (50)	18 (24)	18 (86)	19 (95)	12 (57)
Hypotrichosis	168 (42)	160 (50)	8 (10)	35 (70)	19 (38)	6 (8)	14 (67)	17 (85)	9 (43)
Fragile hair	69 (17)	62 (19)	7 (9)	9 (18)	12 (24)	<3	7 (33)	5 (25)	<3
Alopecia totalis	12 (3)	12 (4)	0	3 (6)	0	0	0	0	3 (14)
Focal alopecia	27 (7)	22 (7)	5 (6)	0	0	10 (13)	<3	<3	<3
Other/not specified	25 (6)[a]	25 (8)	<3	<3	<3	3 (4)	7 (33)	<3	<3
Abnormal eyebrows	114 (29)	108 (34)	6 (8)	29 (58)	16 (32)	<3	3 (14)	8 (40)	8 (38)
Abnormal eyelashes	59 (15)	56 (18)	3 (4)	19 (38)	3 (6)	0	<3	<3	8 (38)
Skin involvement	229 (59)	204 (64)	25 (32)	23 (46)	14 (28)	70 (93)	14 (67)	5 (25)	9 (43)
Dry skin	128 (32)	113 (35)	15 (19)	21 (42)	11 (22)	<3	14 (67)	<3	6 (32)
Eczema	76 (19)	68 (21)	8 (10)	18 (36)	8 (16)	<3	6 (29)	<3	3 (14)
IP lesions	70 (18)	65 (20)	5 (6)	0	0	70 (93)	0	0	0
Thin translucent skin	23 (6)[a]	23 (7)	<3	4 (8)	3 (6)	0	<3	<3	<3
Focal dermal hypoplasia	7 (2)	7 (2)	0	0	0	0	0	0	<3
Palmoplantar keratoderma	16 (4)	13 (4)	3 (4)	<3	0	0	<3	0	<3
Acne vulgaris	8 (2)	8 (3)	0	<3	<3	0	0	<3	0
Other/not specified	43 (11)	38 (12)	5 (6)	3 (6)	5 (10)	3 (4)	<3	<3	<3
Periorbital hyperpigmentation	61 (15)	57 (18)	4 (5)	30 (60)	5 (10)	0	<3	<3	0
Tooth involvement	319 (81)	255 (80)	64 (83)	49 (98)	46 (92)	44 (59)	19 (90)	10 (50)	20 (95)
Hypodontia (1-5 missing teeth)	145 (37)	111 (35)	34 (44)	7 (14)	31 (62)	28 (37)	7 (33)	3 (15)	11 (52)
Oligodontia (≥6 missing teeth)	148 (37)	122 (38)	26 (34)	41 (42)	13 (26)	11 (15)	11 (52)	0	7 (33)
Anodontia	6 (2)	6 (2)	0	<3	<3	0	<3	0	0
Microdontia	4 (1)[a]	4 (1)	<3	0	0	0	0	0	0
Cone-shaped teeth	64 (16)	56 (18)	8 (10)	7 (14)	8 (16)	15 (20)	4 (19)	0	<3
Enamel dysplasia	18 (5)	15 (5)	3 (4)	0	0	<3	0	<3	3 (14)
Other/not specified	16 (4)[a]	16 (5)	<3	<3	0	3 (4)	0	8 (40)	0
Xerostomia (dry mouth)	48 (12)	42 (13)	6 (8)	18 (36)	10 (20)	0	<3	0	0
Nail involvement	105 (27)	93 (29)	12 (16)	4 (8)	5 (10)	12 (16)	10 (48)	8 (40)	6 (29)
Nail dystrophy	96 (24)	84 (26)	11 (14)	3 (6)	5 (10)	12 (16)	10 (48)	7	6 (29)
Anonychia	<3[a]	<3	<3	0	0	<3	0	0	0
Onycholysis	8 (2)	8 (3)	0	0	0	0	0	0	0
Koilonychia	8 (2)	8 (3)	0	<3	0	<3	0	<3	<3
Pachyonychia	8 (2)	8 (3)	0	0	0	0	0	0	3 (14)
Micronychia	5 (1)	5 (2)	0	<3	0	0	0	<3	0
Other/not specified	8 (2)[a]	8 (3)	<3	0	0	<3	0	0	0

(continued)

Table 2. Reported Characteristics of the Cohort and Selected Subgroups of Patients With Confirmed or Likely Ectodermal Dysplasia (continued)

Characteristic	No. (%)								
				Common subgroups					
	All cases	Confirmed cases	Likely cases	Males with XLHED	Females with XLHED	IP	OODD/ SSPS	TRPS	AEC/EEC/ LM/RH syndrome
Eye involvement	70 (17)	64 (20)	6 (8)	5 (10)	<3	22 (29)	0	<3	15 (71)
Dry eyes	15 (4)[a]	15 (5)	<3	3 (6)	<3	<3	0	0	6 (29)
Lacrimal duct dysgenesis	12 (3)	12 (4)	0	0	0	0	0	0	9 (43)
Cataract	6 (2)	6 (2)	<3	<3	0	<3	0	0	<3
Other/not specified	48 (12)	44 (14)	4 (5)	<3	0	21 (28)	0	<3	6 (29)
Hearing loss	20 (5)[a]	20 (6)	<3	<3	<3	<3	0	0	10 (48)
Craniofacial dysmorphology	148 (37)	128 (40)	20 (26)	30 (60)	10 (20)	5 (7)	4 (19)	18 (90)	17 (81)
Tall forehead (high anterior hairline)	30 (8)[a]	30 (9)	<3	8 (16)	3 (6)	0	0	11 (55)	<3
Hypertelorism	6 (2)[a]	6 (2)	<3	3 (6)	0	0	0	<3	0
Low-set, prominent ears	47 (12)	41 (13)	6 (8)	14 (28)	5 (10)	<3	0	4 (20)	5 (24)
Dysplastic ears	8 (2)[a]	8 (3)	<3	0	<3	0	0	<3	<3
Midfacial hypoplasia	51 (13)	43 (13)	8 (10)	19 (38)	5 (10)	0	<3	<3	4 (19)
Facial asymmetry	8 (2)[a]	8 (3)	<3	0	0	<3	<3	0	<3
Bulbous nose	29 (7)	26 (8)	3 (4)	3 (6)	0	0	0	18 (90)	<3
Long philtrum	12 (3)	12 (4)	0	0	0	0	0	11 (55)	0
Cleft lip and/or palate	13 (3)[a]	13 (4)	<3	0	0	0	<3	0	11 (52)
Thick/everted lower lip	19 (5)	16 (5)	3 (4)	8 (16)	<3	0	0	<3	0
Retrognathia	12 (3)	9 (3)	3 (4)	4 (8)	0	0	0	0	<3
Other/not specified	40 (10)	37 (12)	3 (4)	10 (20)	<3	3 (4)	<3	<3	3 (14)
Breast aplasia	12 (3)	12 (4)	0	0	3 (6)	<3	0	0	4 (19)
Nipple aplasia (athelia)	6 (2)[a]	6 (2)	<3	<3	0	0	0	0	<3
Skeletal malformation	53 (13)	42 (13)	11 (14)	0	<3	3 (4)	<3	16 (80)	9 (43)
Syndactyly	18 (5)	11 (3)	7 (9)	0	0	<3	0	<3	4 (19)
Clinodactyly	20 (5)[a]	20 (6)	<3	0	0	<3	0	15 (75)	<3
Brachydactyly	6 (2)	6 (2)	<3	0	0	<3	0	<3	0
Ectrodactyly (split hand/foot)	8 (2)[a]	8 (3)	<3	0	0	0	0	0	6 (29)
Other/not specified	9 (2)[a]	9 (3)	<3	0	<3	<3	<3	<3	<3
Growth retardation	29 (7)	21 (7)	8 (11)	<3	<3	<3	0	10 (50)	<3
Intellectual disability	21 (5)	18 (6)	3 (4)	<3	0	6 (8)	0	<3	3 (14)
Congenital heart anomaly	6 (2)[a]	6 (2)	<3	0	0	0	0	3 (15)	0
Immunodeficiency	4 (1)	4 (1)	0	0	<3	0	0	0	<3
Psychiatric comorbidity	31 (8)[a]	31 (10)	<3	<3	3 (6)	6 (8)	<3	0	3 (15)

Abbreviations: AEC, ankyloblepharon-ectodermal defects-cleft lip/palate; DNPR, Danish National Patient Registry; EEC, ectrodactyly, ectodermal dysplasia, and cleft lip/palate; IP, incontinentia pigment; LM, limb mammary; NA, not applicable; OODD, odontoonychodermal dysplasia; RH, Rapp-Hodgkin; SSPS, Schöpf-Schulz-Passarge syndrome; TRPS, trichorhinophalangeal syndrome; XLHED, X-linked hypohidrotic ectodermal dysplasia.

[a] Small sample sizes (<3) were omitted from totals when required to obscure the values.

prevalence estimates. We considered the age at diagnosis (Table 2) to support the 1995 to 2011 estimate, allowing for a 10-year delay. The prevalence estimate restricted to 1995 to 2001 was slightly higher; however, this short period contained 2 outliers (Figure 2).

We found a prevalence of XLHED at birth of 2.8 cases per 100 000 live births. Another registry-based Danish study, conducted in 2012, reported a prevalence of 4.2 per 100 000 based on molecularly confirmed cases and clinically diagnosed HED, including cases registered with the *ICD-10* code Q82.4.[9] However, that unvalidated case definition may have overestimated results, given the limited validity it showed in our study (PPV = 71.5%). In contrast to our study methods, the 2012 study[9] may have included female carriers of an *EDA* variant that did not fulfill a clinical diagnosis of ED.[1]

Coding Quality

The low PPVs of ED diagnoses in our sample emphasize the importance of diagnosis validation in registry-based studies of rare diseases given that even a small number of misclassified cases can greatly affect associations of interest.[25,26] The low validity of specific *ICD* diagnosis codes for ED in the DNPR may simply be affected by the rarity of ED in the background population.[19,27] However, the common coding of Gorlin-Goltz syndrome and spastic tetraplegia as EDs was noticeable and represents true miscoding.

Several types of EDs do not have a designated *ICD-10* code (eg, trichorhinophalangeal syndrome and ankyloblepharon-ectodermal defects cleft lip/palate syndrome) and may be missed if not registered with an *ICD-10* code for ED unspecified. Furthermore, not all physicians are aware of the specific

ICD-10 ED codes or will use broader codes (eg, Z84.0, the code for "family history of diseases of the skin and subcutaneous tissue"). We tried to mitigate for these missed cases by using several data sources and broad feature-based search algorithms, which revealed a sensitivity of 83.1% for the use of ED-specific *ICD-10* codes only. This type of omission emphasizes the importance of dedicated disease classifications for rare diseases (ie, ORPHAcode and OMIM).[28,29]

Patient Characteristics

Our findings on clinical characteristics in patients with ED highlight the heterogeneity of EDs, which was also underscored by the many different specialties involved. This knowledge can support clinicians in providing diagnostic services and care for patients with ED. Notably, a large proportion (29 of 50) of female patients with *EDA* variants in our cohort also had 2 or more ectodermal features. Although symptoms were generally milder among females than males with XLHED, clinicians and geneticists should be aware of clinical presentations in female relatives.[15,30] We identified a female predominance (62.1%) in the cohort that may partly be influenced by the nature of incontinentia pigmenti (X-linked), with most *IKBKG* variants being lethal in males.

We noticed different patient pathways in the health care system in Denmark. Some patients were referred by a general practitioner to a hospital clinic. Other patients were referred by a local dentist to a maxillofacial department. In the centralized units, some were only evaluated by a dental specialist, and not all were referred to a genodermatosis clinic as part of the diagnostic process. Some patients were diagnosed in adulthood, whereas more severe cases of ED were often diagnosed at birth or during early childhood. A genetic diagnosis was made in 61% of the cases in our study, and only 27% of patients had visited a clinical genetics department. Given the importance of molecular genetics in the current ED classification,[3] the importance of genetic evaluation to support timely and accurate diagnosis of ED cannot be overstated.

The low PPVs and range of medical specialties involved underscore the importance of consensus on ED diagnostic and treatment guidelines that ensure a uniform but still multidisciplinary approach. Furthermore, awareness of the diagnosis among primary health care practitioners is important for proper ED diagnosis and early referral to a rare disease or genodermatosis clinic.

Strengths and Limitations

The use of a nationwide population-based design within a universal health care system, broad search algorithms, multiple data sources, and diagnosis validation constitute key strengths of this study. We had a high validation rate (94%), and it is unlikely that missingness of records depended on case validity.

Our study also had limitations. Prevalence estimates represent a minimum proportion because we may have missed mild ED cases without hospital or health care visits, as well as patients with rare subtypes, and patients deceased before proper diagnosis. Only 1 author validated all the patients included in the study; however, we applied consensus agreement to uncertain cases to minimize potential misclassification. We did not perform a systematic clinical evaluation of all putative cases; therefore, some may have been misclassified with only 1 affected ectodermal derivate, possibly underestimating the true prevalence. Although misclassification and missing medical records may have excluded some ED cases, we estimated that this bias did not substantially affect the prevalence estimate. Given that frequencies of specific features (Table 2) are based solely on positive findings noted in the patient record, they also represent minimum estimates. Not all patients had undergone genetic testing (74%), and the diagnostic yield was incomplete (61%). A genetic diagnosis for all patients would have definitively supported validation; however, the absence of these results reflects clinical practice.

Conclusions

The findings of this nationwide population-based cohort study indicate that ED prevalence is lower than previously reported. The establishment of a large nationwide cohort of patients with ED, including detailed clinical and molecular data, provides a unique resource for future research in ectodermal dysplasias. The low PPVs and incomplete identification of ED using the *ICD-10* codes in our study emphasize the importance of ED diagnosis validation and accurate disease registration.

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REFERENCES

1. Wright JT, Fete M, Schneider H, et al. Ectodermal dysplasias: classification and organization by phenotype, genotype and molecular pathway. *Am J Med Genet A*. 2019;179(3):442-447. doi:10.1002/ajmg.a.61045

2. Freire-Maia N. Ectodermal dysplasias. *Hum Hered*. 1971;21(4):309-312. doi:10.1159/000152419

3. Peschel N, Wright JT, Koster MI, et al. Molecular pathway-based classification of ectodermal dysplasias: first five-yearly update. *Genes (Basel)*. 2022;13(12):2327. doi:10.3390/genes13122327

4. Visinoni AF, Lisboa-Costa T, Pagnan NA, Chautard-Freire-Maia EA. Ectodermal dysplasias: clinical and molecular review. *Am J Med Genet A*. 2009;149A(9):1980-2002. doi:10.1002/ajmg.a.32864

5. Pagnan NA, Visinoni ÁF. Update on ectodermal dysplasias clinical classification. *Am J Med Genet A*. 2014;164A(10):2415-2423. doi:10.1002/ajmg.a.36616

6. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet C Semin Med Genet*. 2004;131C(1):45-51. doi:10.1002/ajmg.c.30033

7. McKusick VA. *Mendelian inheritance in man: a catalog of human genes and genetic disorders*. 12th ed. Johns Hopkins University Press; 1998. doi:10.56021/9780801857423

8. Jorgenson RJ. Ectodermal Dysplasia, Christ-Siemens-Touraine type. In: Buyse ML, ed. *Birth Defects Encyclopedia*. Blackwell; 1990:597-598.

9. Nguyen-Nielsen M, Skovbo S, Svaneby D, Pedersen L, Fryzek J. The prevalence of X-linked hypohidrotic ectodermal dysplasia (XLHED) in Denmark, 1995-2010. *Eur J Med Genet*. 2013;56(5):236-242. doi:10.1016/j.ejmg.2013.01.012

10. Geirdal AØ, Saltnes SS, Storhaug K, Åsten P, Nordgarden H, Jensen JL. Living with orofacial conditions: psychological distress and quality of life in adults affected with Treacher Collins syndrome, cherubism, or oligodontia/ectodermal dysplasia-a comparative study. *Qual Life Res*. 2015;24(4):927-935. doi:10.1007/s11136-014-0826-1

11. Saltnes SS, Jensen JL, Sæves R, Nordgarden H, Geirdal AØ. Associations between ectodermal dysplasia, psychological distress and quality of life in a group of adults with oligodontia. *Acta Odontol Scand*. 2017;75(8):564-572. doi:10.1080/00016357.2017.1357189

12. Blüschke G, Nüsken KD, Schneider H. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Early Hum Dev*. 2010;86(7):397-399. doi:10.1016/j.earlhumdev.2010.04.008

13. Mark BJ, Becker BA, Halloran DR, et al. Prevalence of atopic disorders and immunodeficiency in patients with ectodermal dysplasia syndromes. *Ann Allergy Asthma Immunol*. 2012;108(6):435-438. doi:10.1016/j.anai.2012.04.010

14. Fete T. Respiratory problems in patients with ectodermal dysplasia syndromes. *Am J Med Genet A*. 2014;164A(10):2478-2481. doi:10.1002/ajmg.a.36600

15. Wohlfart S, Meiller R, Hammersen J, et al. Natural history of X-linked hypohidrotic ectodermal dysplasia: a 5-year follow-up study. *Orphanet J Rare Dis*. 2020;15(1):7. doi:10.1186/s13023-019-1288-x

16. Frank L. Epidemiology: when an entire country is a cohort. *Science*. 2000;287(5462):2398-2399. doi:10.1126/science.287.5462.2398

17. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/CLEP.S179083

18. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

19. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

20. Nygaard N, Ängquist L, Belstrøm D, et al. The national child odontology registry (SCOR): a valuable resource for odontological and public health research. *BMC Oral Health*. 2023;23(1):608. doi:10.1186/s12903-023-03199-1

21. Sundhedsdatastyrelsen. Sundhedsvæsenets Klassifikations System. SKS-browser. Accessed February 9, 2024. https://medinfo.dk/sks/brows.php

22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

23. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208

24. Statistics Denmark. Accessed July 4th, 2023. https://www.statistikbanken.dk/

25. Jørgensen LK, Dalgaard LS, Østergaard LJ, Andersen NS, Nørgaard M, Mogensen TH. Validity of the coding for herpes simplex encephalitis in the Danish National Patient Registry. *Clin Epidemiol*. 2016;8:133-140. doi:10.2147/CLEP.S104379

26. Kristensen MH, Schmidt SAJ, Kibsgaard L, Mogensen M, Sommerlund M, Koppelhus U. Validity of first-time diagnoses of congenital epidermolysis bullosa in the Danish National Patient Registry and the Danish Pathology Registry. *Clin Epidemiol*. 2019;11:115-124. doi:10.2147/CLEP.S184742

27. Brenner H, Savitz DA. The effects of sensitivity and specificity of case selection on validity, sample size, precision, and power in hospital-based case-control studies. *Am J Epidemiol*. 1990;132(1):181-192. doi:10.1093/oxfordjournals.aje.a115630

28. Rath A, Olry A, Dhombres F, Brandt MM, Urbero B, Ayme S. Representation of rare diseases in health information systems: the Orphanet approach to serve a wide range of end users. *Hum Mutat*. 2012;33(5):803-808. doi:10.1002/humu.22078

29. Hamosh A, Amberger JS, Bocchini C, Scott AF, Rasmussen SA. Online Mendelian Inheritance in Man (OMIM): Victor McKusick's magnum opus. *Am J Med Genet A*. 2021;185(11):3259-3265. doi:10.1002/ajmg.a.62407

30. Fete M, Hermann J, Behrens J, Huttner KM. X-linked hypohidrotic ectodermal dysplasia (XLHED): clinical and diagnostic insights from an international patient registry. *Am J Med Genet A*. 2014;164A(10):2437-2442. doi:10.1002/ajmg.a.36436