Clinical Findings in Mosaic Carriers of Hypohidrotic Ectodermal Dysplasia

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Background: Hypohidrotic ectodermal dysplasia (HED) is a severe developmental disorder in which nonallelic genetic heterogeneity has been demonstrated. Even though X-linked and autosomal recessive forms are phenotypically similar, identification of the way of transmission is mandatory to give reliable genetic counseling to the family and to address molecular studies. Complete examination of relatives of patients with HED and identification of carriers of partial forms of the disorder in their families is the key to clarifying intrafamilial genetic transmission.

Observations: Seven patients diagnosed as having HED and their first-degree relatives were carefully examined and tested with starch-iodine. Useful signs for identifying possible carriers of and postzygotic mosaics for X-linked HED and for finding distinctive features between the X-linked and the autosomal recessive forms of the disorder were recorded. Of these, the most striking finding was the clinical evidence of the distribution of normal and abnormal skin along Blaschko lines in heterozygous and postzygotic mutation carriers of X-linked HED. Six heterozygous female carriers of X-linked HED, 2 males with postzygotic mutations for X-linked HED, and 1 female with autosomal recessive HED were clinically identified. At the end, 6 families had a diagnosis of X-linked HED, while 1 had a diagnosis of autosomal recessive HED. Clinical data, family history, and starch-iodine test results were never in conflict in the 7 families.

Conclusions: Careful clinical examination is the best way to detect heterozygous carriers and postzygotic mutation of X-linked HED. Heterozygous parents of patients with autosomal recessive HED show no features of the disorder. The starch-iodine test is not superior to a clinical examination in heterozygous carrier detection but may play a confirmative role and be of help in differentiating X-linked and autosomal recessive HED in isolated patients.

Arch Dermatol. 2000;136:217-224

ECTODERMAL dysplasias are developmental disorders affecting tissues of ectodermal origin. Hypohidrotic ectodermal dysplasia (HED) (also called anhidrotic ectodermal dysplasia or Christ-Siemens-Touraine syndrome) features a defect in the hair, in the teeth, and in mucosal and sweat glands. The inability to sweat is responsible for the most dangerous consequences of the disorder, ie, life-threatening and brain-damaging episodes of hyperthermia. Two different ways of transmission of the disorder are known. Along with the more common X-linked recessive modality of transmission, a less frequent autosomal recessive one has been demonstrated. In X-linked HED, the affected patients are most often hemizygous male subjects, since in heterozygous female carriers the severity of the disorder varies considerably; most females only have a mild or “partial” involvement and are most often not referred to the physician. Autosomal recessive HED is similar to the hemizygous form of X-linked HED from the clinical point of view except that males and females are equally affected. The gene responsible for X-linked HED is localized at Xq12-q13.1 and affects a transmembrane protein expressed by keratinocytes, hair follicles, and sweat glands, possibly having a key role in epithelial-mesenchymal signaling. A gene responsible for autosomal HED has recently been mapped to chromosome 2q11-q13.

We describe the clinical findings and the results of starch-iodine testing in 7 new families with HED to further delineate useful signs in heterozygous carrier detection and to find possible clues to clinically differentiate between the X-linked and the autosomal recessive forms.

RESULTS

Four mothers of male probands (mothers 1, 2, 3, and 7) (Table) were considered heterozygous for the X-linked HED gene af-
PATIENTS AND METHODS

PROBANDS WITH HED

Figure 1 summarizes the clinical and genetic data of the probands and their first-degree relatives. Seven children (3 males and 2 females) were diagnosed as having HED by medical history and typical clinical findings. In all probands except 1 (female proband 6 in Figure 1), typical facial features, hypotrichosis, anodontia with abnormally shaped teeth, hypohidrosis, heat intolerance, and recurrent respiratory tract infections were recorded. Female proband 6 lacked heat intolerance and respiratory tract infections. All the parents and siblings of the probands were examined, and thorough personal and familial histories were obtained. In no other member of the probands’ families had a previous diagnosis of HED been made, except for the maternal grandfather of proband 7.

CLINICAL MANIFESTATIONS IN MOTHERS OF PROBANDS WITH HED

Family histories being negative, 6 of 7 mothers were not considered as obligate carriers of the disorder at the time of examination. The 2 mothers of the female probands and the mother of a male proband showed no signs or symptoms related to HED. On the other hand, in 4 mothers of male probands, minor signs of HED were found at clinical examination and by obtaining the medical history. The findings in these 4 women (mothers 1, 2, 3, and 7) are summarized in the Table.

CLINICAL MANIFESTATIONS IN FATHERS OF PROBANDS WITH HED

None of the fathers showed any signs or symptoms related to HED except for the father of female proband 6. He had a peg-shaped incisor and the absence of 2 dental germ layers (1 incisor and 1 premolar), mildly everted lips, and stripes of atrichia on the limbs. No other features were evident. Scalp hypotrichosis was reported but could not be evaluated owing to the presence of androgenetic alopecia.

CLINICAL MANIFESTATIONS IN SIBLINGS OF PROBANDS WITH HED

All the probands were only children except 2 (in families 6 and 7 in Figure 1). The brother of proband 6 showed no signs or symptoms related to HED, while in 1 of the 2 sisters of proband 7 minor signs of HED were found at clinical examination (the elder sister in the Table).

STARCH-IODINE TESTING

The starch-iodine test was used to observe the distribution of actively secreting sweat glands. The mothers of all probands, the fathers of the 2 female probands, the sisters of proband 7, and female proband 5 and male proband 7 themselves (who were aged 5 and 7 years, respectively, at the time) were tested. The test was not performed in most of the probands because of fear of malaise after heat exposure and of lack of cooperation, since they were younger than 4 years. None of the tested subjects had thyroid gland disorders in their medical history.

A slightly modified Wada technique was used. The whole backs of the tested subjects were painted with a solution containing 2% iodine in absolute alcohol. This was allowed to dry, and after some minutes a layer of a compound of maize starch in peanut oil (100 g/100 mL) was painted over it. The subjects were then moved to a high-temperature room previously warmed with electric heaters. Active sweat pores were evidenced by the appearance of minute dark spots as a consequence of the reaction between starch and iodine in the presence of water supplied by the sweat droplets. The response as it appeared on the skin was observed by eye and directly photographed for documentation. After the test, a shower allowed the rapid removal of the paintings from the skin.

Normal control subjects showed a uniform distribution of dark spots on their backs. In all the 4 mothers with clinical manifestations of HED, the starch-iodine test results confirmed a mosaic distribution of functional sweat glands with active sweat pores disposed along Blaschko lines (Figure 2). As expected, in the clinically nonaffected mother of male proband 4, the starch-iodine test results showed a uniform distribution of the active sweat glands. Both parents of female proband 5 showed a normal distribution of the active sweat glands when tested. The female proband herself was then tested and showed a nearly total absence of functioning sweat glands on the back, shoulders, and upper arms (nonreactive yellow skin), thus excluding a mosaic distribution of the ectodermal defect in these areas (Figure 3). In the father of female proband 6, the test results demonstrated the linear absence of sweating in correspondence with the stripes of hypotrichosis on his upper limbs, while a mosaic linear distribution of functioning sweat glands was not clearly visible on his back. As expected, male proband 7 showed a total absence of functioning sweat glands when tested. His elder sister showed a linear distribution of functioning sweat glands along Blaschko lines on her back, while in his younger sister the test yielded normal results.

Only 1 of the tested subjects showed an adverse effect of the starch-iodine application. In this patient, the test was performed twice within a short time because of a technical mistake. This caused the appearance of dusky erythematous patches over her back following the second application of the compound.

ter clinical examination and medical history. The diagnosis was confirmed in the 4 women by the starch-iodine test (Figure 2). In 1 of the 4 women, the observation of some family snapshots further confirmed the diagnosis. In fact, despite the woman’s total unawareness, the pictures of her father showed typical HED facial features.

In these 4 heterozygous mothers, some facial features of the disorder were always present but were often difficult to assess, being closer to normal. Dental abnormalities highly suggestive of HED were present in each of the 4 women. Hypotrichosis of scalp hair was clearly evident in 2 of them, while it was not prominent in the other 2. Patchy absence of vellus hair and stripes of hypotrichosis along the limbs and the back were noted in all 4 women. Normal skin containing pilosebaceous units tended to be lighter and slightly elevated in contrast to
xerotic, slightly darker, and depressed skin not containing adnexa. On the back of 3 of these women, these adjacent areas of normal and abnormal skin were found to be disposed along the lines of Blaschko (Figure 4). The visibility of Blaschko lines without the need for the starch-iodine test was the most striking feature in the heterozygous females of this study. Two of the 4 women were conscious of reduced sweating, while 2 were not. Interestingly, 2 heterozygous mothers were said to have abnormal abundant desquamation soon after birth, while their 2 sons with HED presented with mild colloidion “babies” and were thought to have congenital ichthyosis at birth. Curiously, 1 woman had an unusual distribution of pityriasis versicolor, reflecting the abnormal distribution of the pilosebaceous units (Figure 5).

The parents of male proband 4 were considered unaffected after clinical examination. As expected, the starch-iodine test in the mother yielded negative results. The proband might represent a new mutation of the X-linked HED gene or be affected by autosomal recessive HED. The former hypothesis was strongly sustained by the clinical observation of limited areas of apparently normal skin. In particular, the child had some pale skin areas containing adnexa, disposed along Blaschko lines identical to those observed in female proband 6, but in a more limited distribution. A diagnosis of X-linked HED due to an early postzygotic mutation was made. In this patient, a starch-iodine test at an older age and in strictly controlled conditions will confirm the diagnosis by showing the presence of some functioning sweat glands along the lines of Blaschko.

Female proband 5 had a full-blown form of HED, without linear areas of normal skin. She had a normal karyotype, excluding an X; autosomal translocation. Both of her parents showed no clinical sign and no personal or familial history of HED. The starch-iodine test result showed the absence of functioning sweat glands with no mosaic distribution of the disorder in the child (Figure 3) and was normal in both parents. A diagnosis of autosomal recessive HED was made.

Female proband 6 had a mild expression of HED, without heat strokes, unexplained fever, or recurrent respiratory tract infections. An examination of the child revealed linear areas of pale normal skin containing adnexa, intermingled with linear areas of slightly depressed, dry, somewhat darker glabrous skin. A patchy or linear disposition of whitish and slightly raised papules centered by vellus hair was observed on the trunk and limbs (Figure 6). Most strikingly, these linear areas and papular lesions formed a clearly visible pattern of Blaschko lines on her back (Figure 7). Findings in this child are summarized in the Table (proband 6). The father of female proband 6 had some signs of the disorder in a limited distribution. He was regarded as having a postzygotic mutation leading to a mild, partial form of X-linked HED, while his daughter had possibly inherited the X chromosome bearing the mutation from him, thus becoming a heterozygous carrier of X-linked HED.

The elder sister of proband 7 presented with suggestive dental abnormalities and mild alterations in skin texture and body hair arrangement (Table). The latter were similar but much less evident to those observed in probands 4 and 6. The starch-iodine test results confirmed her to be a heterozygous carrier for the X-linked HED gene. A highly skewed X chromosome inactivation was hypothesized to explain her mild clinical features.

Nonallelic genetic heterogeneity of HED has been recently demonstrated. To provide correct genetic counseling to the patients and their families and to correctly address molecular biology research studies, differentiation between X-linked and autosomal forms of HED is required. Even if the clinical diagnosis of the disorder is easy, especially after the first year of life when medical history and clinical findings become highly characteristic, in sporadic cases the differentiation between the 2 genetic forms is not. Hypertelorism, sensorineural hearing loss, mental retardation, and nail dystrophy were suspected to be more typical of autosomal recessive HED, but it is clear that the X-linked hemizygous males and autosomal recessive forms are not phenotypically distinguishable. One of the main tasks in the case of a patient with sporadic HED is to find in the patient’s family other possible carriers of the disorder. To find heterozygous females with X-linked HED or parents with partial manifestations of the disorder due to a postzygotic mutation is the key to clinically differentiating between the X-linked and the autosomal forms of HED.

In a female heterozygous for the X-linked HED gene, the presence of 2 different cell lines due to random inactivation of 1 of the 2 X chromosomes during embryogen-
### Clinical Manifestations in Heterozygous Females With X-linked HED

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29</td>
<td>39</td>
<td>33</td>
<td>35</td>
<td>35</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Facial features</td>
<td>Everted lips and mild periorbital ridging</td>
<td>Everted lips, malposition of large external ears, and saddle nose</td>
<td>Everted lips and prominent chin</td>
<td>Mildly everted lips and periorbital ridging</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Teeth</td>
<td>Absence of 7 germ layers (incisors and molars), peg-shaped incisors, OPT at a young age, and wears dentures</td>
<td>Absence of several germ layers, delayed eruption (at the age of 19 mo), peg-shaped incisors, permanence of primary dentition, and wears dentures</td>
<td>Absence of 4 germ layers (incisors), delayed eruption (at the age of 12 mo), OPT at a young age, and wears dentures</td>
<td>Absence of lower incisors, permanence of primary dentition, and carries at a young age</td>
<td></td>
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<tr>
<td>Scalp hair</td>
<td>Mild hypotrichosis (it was never a problem) and complains of thin and frail hair</td>
<td>Marked hypotrichosis (it has been a great problem since childhood) and complains of thin and sparse hair</td>
<td>Hypotrichosis (since childhood); and complains of thin, towy, and slow-growing hair</td>
<td>Mild hypotrichosis (it was never a problem); hair is thin, long, and curly</td>
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<tr>
<td>Eyebrows and eyelashes</td>
<td>Thin</td>
<td>Sparse (especially eyelashes)</td>
<td>Slightly sparse</td>
<td>Slightly sparse eyebrows</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Body hair</td>
<td>Patchy absence of vellus hair and stripes of hypotrichosis along the limbs and the back</td>
<td>Patchy absence of vellus hair and stripes of hypotrichosis along the limbs and the back</td>
<td>Stripes of hypotrichosis along the limbs and the back</td>
<td>Patchy absence of vellus hair and stripes of hypotrichosis along the limbs and the back</td>
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<tr>
<td>Sweating</td>
<td>Always been aware of partial sweating (&quot;not at all at the face, \ldots&quot;); improvement in adult life and after pregnancy referred</td>
<td>Always been aware of poor sweating; improvement in adult life referred</td>
<td>Not aware of any diminished sweating</td>
<td>Not aware of any diminished sweating</td>
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<tr>
<td>Complaints of malaise after heat exposure</td>
<td>Refers to no problems but remembers 2 to 3 episodes of episthymia in a warm climate</td>
<td>Refers to feeling uncomfortable in a warm climate</td>
<td>Refers to no peculiar problems</td>
<td>Refers to feeling uncomfortable in a warm climate</td>
<td></td>
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<tr>
<td>Respiratory tract infections</td>
<td>Otitis media frequent in the first years of life</td>
<td>Frequent at a young age</td>
<td></td>
<td></td>
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<tr>
<td>Nasal crustung and others</td>
<td>Had epistaxis (required cauteronization)</td>
<td>\ldots</td>
<td>\ldots</td>
<td>\ldots</td>
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<tr>
<td>Xerostomia</td>
<td>Referred to at night</td>
<td>\ldots</td>
<td>\ldots</td>
<td>\ldots</td>
<td>Yes (using antihistaminic drugs for asthma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of eczematous and atopic disorders</td>
<td>Diaper dermatitis in childhood</td>
<td>Episodes of asthma at a young age</td>
<td>Atopic dermatitis at a young age and presently has a mild form of asthma</td>
<td></td>
<td></td>
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<tr>
<td>Xerotic skin</td>
<td>\ldots</td>
<td>Yes</td>
<td>Yes (using ointments)</td>
<td>Yes (using ointments)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Problems in the neonatal period</td>
<td>Abnormal desquamation referred</td>
<td>\ldots</td>
<td>Abnormal desquamation of the left side of the body referred</td>
<td>\ldots</td>
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<tr>
<td>Mammary abnormalities</td>
<td>Unable to suckle for &quot;hollow nipples&quot;</td>
<td>Poor bilateral breast development, but suckling was not a problem</td>
<td>Mild hypoplasia of the left breast and hollow nipples (problems in suckling?)</td>
<td>Mild hypoplasia of the left breast; she was unable to suckle from this side for hollow nipple</td>
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<tr>
<td>Constipation</td>
<td>Constant at a young age</td>
<td>\ldots</td>
<td>\ldots</td>
<td>\ldots</td>
<td>\ldots</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Result of the starch-iodine test</td>
<td>Functioning sweat glands disposed along Blaschko lines on the back</td>
<td>Functioning sweat glands disposed along Blaschko lines on the back</td>
<td>Functioning sweat glands disposed along Blaschko lines on the back</td>
<td>Functioning sweat glands disposed along Blaschko lines on the back</td>
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</tr>
<tr>
<td>Others</td>
<td>Pityriasis versicolor in a bizarre distribution, occipital protuberance, and erythematous patches after the starch-iodine test</td>
<td>Vitiligo, awareness of having a bizarre drawing on her back, and South American origin</td>
<td>Awareness of having the drawing &quot;of a tree&quot; over her back, that was more visible in childhood and after suntanning</td>
<td>She was not aware of having a drawing over her back, but her husband had noted &quot;bizarre lines&quot;</td>
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</tbody>
</table>

*Heat strokes, unexplained fever, seizures, dry eyes, photophobia, absence of lacrimation, nail abnormalities, impacted cerumen formation, and clinodactyly were not noted in any of these females. HED indicates hypohidrotic ectodermal dysplasia; OPT, orthopantograph; and ellipses, no findings.*
carriers of X-linked HED by clinical examination was calculated by Pinheiro and Freire-Maia\textsuperscript{16,17} as being between 60% and 70%. In fact, the symptoms of females are generally minor and not of medical interest, and although affected females outnumber affected males, often close female relatives of the male probands are not studied or are only superficially examined.\textsuperscript{18} Thus, mild

dentis abnormalities, mild hypohidrosis, and mild hypotrichosis are the most commonly described signs in female carriers of X-linked HED.\textsuperscript{17} The reported studies on this matter have rarely focused their attention on abnormalities of the skin texture. Kerr et al\textsuperscript{20} considered the findings of partial anodontia and diminished activity of the sweat glands as important diagnostic clues in heterozygous females with X-linked HED, while they detected no scalp or body hair abnormalities.
Verbov studied the families of 5 affected male patients, supplementing medical history and clinical examination with different diagnostic methods such as sweat testing, plastic imprinting, sweat pore counting, and dermatoglyphic analysis, obtaining conflicting and uncertain results on gene carrier detection. Pinheiro and Freire-Maia analyzed a large X-linked HED Brazilian kindred with 27 carriers and noted 2 peculiar and characteristic signs in heterozygous female patients: (1) a mosaic patchy distribution of body hair, ie, areas of skin containing normal body hair sided by areas where hair is absent; and (2) radial deviation of distal phalanges of the index fingers. Clarke et al studied 57 obligate female carriers of 22 families with X-linked HED. The researchers focused their attention on heat intolerance, abnormalities in teeth and scalp hair, and medical history but failed to report any evidence of visible abnormalities in the skin of female carriers.

In the present study, a careful clinical examination and a medical history were sufficient to determine that 4 mothers and 1 sister of male probands with HED and an additional female proband were heterozygous carriers of the X-linked gene defect (Table). In our 6 heterozygous females with X-linked HED, teeth abnormalities were the most constant marker of the disorder. These could have gone unnoticed in the adult females since they all wore dentures. Dental abnormalities are to be considered a key feature since they are easily noted at a young age and should lead to diagnostic suspicion, as was the case in the elder sister of proband 7. None of the heterozygous subjects had the typical HED facial features but often showed some mild facial signs of the disorder that could be noticed, keeping a high index of suspicion. Scalp hair is typically thin and light in heterozygous subjects but, as observed in other clinical reports, the degree of scalp hypotrichosis is highly variable (Table). Hypohidrosis is only partial in these subjects and may not be prominent; however, 3 of 6 heterozygous females in this study were aware of reduced sweating. Curiously, 2 of the heterozygous mothers reported an improvement of hypohidrosis in adult life. Although bizarre, this is probably not such an uncommon event, since Verbov also reported that 2 mothers of patients with HED stated that they had not sweated normally “in childhood.” Nail dystrophy was observed neither in probands with HED nor in heterozygous carriers in the 7 examined families. It is clear that nail dystrophy is not a feature of true HED, although the disorder has been classified in the 1-2-3-4 ectodermal dysplasia subgroup according to the classification of Freire-Maia and Pinheiro. In the 6 heterozygous females with X-linked HED, no life-threatening or most serious manifestations of the disorder, such as severe respiratory tract infections, heat strokes, or episodes of unexplained high fever, were recorded. Radial deviation of the distal phalanges of the index fingers was absent in all subjects.

We found patchy distribution of vellus body hair in all our 6 females determined to be heterozygous carriers of X-linked HED. This is a sign to be looked for carefully, since vellus hair is not easily observed in children, while adult women may epilate their limbs. The patchy distri-
The distribution was more easily observed on the back and thighs. The areas of presence and absence of skin adnexa are not randomly distributed or simply patchy but follow the lines of Blaschko. The typical linear Blaschko pattern of the back was evident in 4 of the 6 heterozygous female carriers of X-linked HED even before the starch-iodine test was performed (Figure 4). When specifically asked, these females (or their relatives) were conscious of having “a bizarre drawing” or “the drawing of a tree” on their back. The drawing can be seen when looking at the naked patient from a certain distance and under different light sources (incident rays are particularly useful). Normal skin is paler, contains vellus hair, and looks slightly more elevated, while abnormal skin looks somewhat slightly depressed, is dryer, and does not contain hair follicles. The linear distribution was reported to be more visible after suntanning and during infancy. In proband 6 (a female child), the linear distribution of normal skin sometimes assumed a whitish micropapular appearance, the pale papules containing the adnexa and coalescing into stripes (Figures 6 and 7). The 2 female carriers in whom this drawing was not noticed (mother 1 and the elder sister of proband 7) had a clear skin complexion, and we wonder if we have looked for this sign carefully enough.

Partial involvement with either normal or abnormal skin disposed along Blaschko lines was also observed in 2 males (proband 4 and the father of female proband 6). This finding allowed the diagnosis of a postzygotic mutation for the X-linked HED gene in these 2 subjects. Considering the different extension of the cutaneous involvement, an early and a later mutation were diagnosed in the child (male proband 4) and in the father of proband 6, respectively.

Distribution of the functioning eccrine sweat glands along Blaschko lines in patients heterozygous for X-linked HED may be easily revealed with the starch-iodine test. The starch-iodine technique allows the testing of a wide surface, and the use of a large body area such as the back reduces the possibility of missing a mosaic distribution of the disorder.11,14 Moreover, Blaschko lines have a peculiar arrangement on the trunk, so that starch-iodine testing is to be preferred to plastic imprints of the palmar surface.21 In our study, sweat testing with the starch-iodine technique on a large cutaneous surface was used as a control proof for the clinical diagnosis of heterozygous X-linked HED. As expected, in the female relatives of male probands with HED featuring signs of HED, the starch-iodine test spectacularly drew the lines of Blaschko, whereas in the others it did not. In contrast to previous reports,14,15 starch-iodine only had a confirmative role but was not superior to clinical diagnosis in heterozygous carrier detection. As shown by the father of female proband 6, the test easily reveals an abnormal distribution of functioning sweat glands in those body sites that also show the clinical evidence of an abnormal skin texture.

As previously demonstrated,11 the starch-iodine test is helpful in differentiating autosomal recessive and X-linked HED in isolated patients. In autosomal recessive HED, the patients, males and females, have a full-blown phenotype of the disorder. Nothing is known about clinical manifestations in heterozygous carriers of autosoma-
mal recessive HED. Female proband 5 in our study had full-blown HED with no linear distribution of the disorder at clinical examination; she was suspected to have autosomal recessive HED. In her case, the starch-iodine test results showed a nearly complete absence of functioning sweat glands. Both of her parents had neither clinical evidence of the disorder nor abnormalities according to the starch-iodine test. Our results suggest that heterozygous carriers of autosomal recessive HED do not have partial manifestations of the disorder unlike heterozygous carriers of X-linked HED. A full-blown disorder in a female patient, equally affected males and females in a single sibship, and the presence of parental consanguinity increase suspicion of the autosomal recessive form of HED.3 In the isolated patient, the lack of linear areas of affected and normal skin after clinical and starch-iodine examinations and the absence of any sign of the disorder in the parents should be highly suggestive of autosomal recessive HED.

In conclusion, although obtained in a small number of families, our results suggest that heterozygous female carriers of X-linked HED detected with the starch-iodine technique as a rule have some clinical evidence of the disorder when carefully examined. Moreover, a careful clinical examination may allow differentiation between X-linked and autosomal forms of HED and the detection of signs of the disorder in a mosaic distribution in male patients with a postzygotic mutation of the X-linked HED gene. The starch-iodine test is a simple, noninvasive method for further confirming the diagnosis and is a useful tool in isolated patients for differentiating homozygous females with autosomal recessive HED from heterozygous females with X-linked HED. Clinical data, family history, and starch-iodine test results were never in conflict in our 7 families.

Since this article was accepted for publication, 3 of the 7 families (families 1, 6, and 7) underwent molecular evaluation for their disorder. In these 3 families, mutations of the EDA1 gene responsible for X-linked HED were demonstrated by direct mutational analysis, confirming our clinical clues. Moreover, the father of proband 6 was confirmed to be heterozygous for his gene mutation, confirming the mosaic state of his genetic defect. The complete data of the genetic studies will be published elsewhere.

Accepted for publication August 23, 1999.

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