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Evidence of the high prevalence of neurological disorders in nonsyndromic X-linked recessive ichthyosis: a retrospective case series*

B. Rodrigo-Nicolás,[1] E. Bueno-Martínez,[2] A. Martín-Santiago,[3] J. Cañueto,[4] A. Vicente,[5] A. Torrelo,[1] L. Noguera-Morel,[1] A. Duat-Rodríguez,[6] C. Jorge-Finnigan,[1] I. Palacios-Álvarez,[1] J.L. García-Hernández,[2] D.F. Sebaratnam,[1] R. González-Sarmiento[2] and A. Hernández-Martín[1]

Departments of [1]Dermatology and [6]Neurology, Hospital Infantil Niño Jesús, Madrid, Spain
[2]Molecular Medicine Unit-Department of Medicine, IBSAL and IBMCC and University Hospital of Salamanca, CSIC, University of Salamanca, Spain
[3]Department of Dermatology, Hospital Son Espases, Palma de Mallorca, Spain
[4]Department of Dermatology, Hospital Universitario de Salamanca, Salamanca, Spain
[5]Department of Dermatology, Hospital Sant Joan de Deu, Barcelona, Spain

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Summary

Background X-linked recessive ichthyosis (XLI) is a relatively common type of ichthyosis caused by a deficiency in the steroid sulfatase (STS) enzyme. It is the only type of ichthyosis that can be both syndromic and nonsyndromic. Typical clinical features include dark-brown scale of variable size favouring the extensor surfaces of the extremities.

Objectives To characterize clinically nonsyndromic XLI, with a particular focus on extracutaneous manifestations.

Methods This was a multicentre retrospective review of clinical findings from a case series of patients with a clinical and genetic diagnosis of XLI.

Results We identified 30 patients with XLI belonging to 25 different families carrying a deletion in the STS locus. All patients had dark scales of variable size on the extensor surfaces of the extremities. Lack of flexural involvement and pruritus were common but inconsistent findings, whereas palmoplantar hyperlinearity was absent in all but one patient. A history of orchiopexy was present in 10% and thus was more common than expected vs. the general population (3%). Neurological disorders including epilepsy (13%) and attention deficit hyperactivity disorder (ADHD; 30%) were over-represented in patients with XLI.

Conclusions This was a retrospective study with a limited number of patients. In the absence of confirmatory genetic testing and family history of the disease, dark-brown scale of the extensor surfaces and the absence of palmoplantar hyperlinearity appear to be the most reliable clinical findings supporting a diagnosis of XLI. Dermatologists should be aware of the high prevalence of ADHD and epilepsy in patients with nonsyndromic XLI.

Correspondence
Angela Hernández-Martín and Rogelio González-Sarmiento.
E-mails: ahernandez@aedv.es and gonzalez@usal.es

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Current affiliation for B.R-.N.: Department of Dermatology, Hospital Universitario de La Plana, Vila-real, Castellón, Spain. Current affiliation for C.J.-F.: Hospital de los Santos Reyes, Aranda de Duero, Burgos, Spain. Current affiliation for D.F.S.: Faculty of Medicine University of New South Wales Sydney, Sydney, Australia. Current affiliation for I.P.-A.: Department of Dermatology of Clínica Universidad de Navarra, Pamplona, Spain.

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What's already known about this topic?

- Nonsyndromic X-linked recessive ichthyosis is a relatively common type of ichthyosis.
- Prior studies found a high prevalence of cryptorchidism and attention deficit hyperactivity disorder (ADHD).

What does this study add?

- We identified a high prevalence of epilepsy (13%), confirmed a high frequency of ADHD (30%) and found a 10% prevalence of orchiopexy.

- We also quantified other common findings such palmoplantar hyperlinearity (almost always absent) and pruritus (present in 60% of patients).

X-linked recessive ichthyosis (XLI) is a relatively common type of ichthyosis affecting one in 3000–8000 individuals.[1,2] After ichthyosis vulgaris, XLI is the most common form of ichthyosis.[3,4] It most commonly affects males; females are asymptomatic disease carriers. However, exceptional cases of XLI in women have been reported.[5–7]

The condition is caused by deficiency of the steroid sulfatase (STS) enzyme, whose gene is mapped to the distal part of the short arm of the X chromosome (Xp22·3).[8] STS is a microsomal enzyme expressed in the central nervous system, liver, adrenal cortex, placenta, gonads, skin and leucocytes, and is responsible for the hydrolysis of the 3β-sulfate esters.[9] In the epidermis, STS deficiency results in a concentration of cholesterol sulfate in the stratum corneum 10 times higher than normal.[2] Accumulation of cholesterol sulfate in the epidermis inhibits proteases such as kallikrein 5 and kallikrein 7, which are essential for normal degradation of corneodesmosomes and physiological desquamation.[10]

XLI usually appears during early infancy and shows typical features, including dark-brown scale of variable size favouring the extensor surfaces of the extremities. Scalp desquamation is also common, as well as dark scaling on the lateral face and neck, which gives patients a 'dirty' appearance (Fig. 1).[3] Patients with XLI with associated filaggrin gene mutations (*FLG*) may show a more severe phenotype and more frequent cutaneous infections.[11,12]

XLI is the only type of ichthyosis that can be both syndromic and nonsyndromic, depending the presence of extracutaneous manifestations.[4] Although clinical diagnosis is relatively simple in most cases, genetic testing of *STS* may occasionally be necessary to distinguish XLI from other types of ichthyosis, particularly with regard to ichthyosis vulgaris in males when there is no family history of the disease.

We sought to better define the clinical findings of XLI in a cohort of patients with genetically confirmed disease, with a particular focus on extracutaneous manifestations of the disease.

Patients and methods

We performed a multicentre retrospective review of all patients with a clinical and genetic diagnosis of XLI seen at four tertiary hospitals across Spain – Hospital Infantil Niño Jesús (Madrid), Hospital Son Espases (Palma de Mallorca), Complejo Hospitalario de Salamanca (Salamanca) and Hospital Sant Joan de Deu (Barcelona) – between 1 January 1983 and 31 December 2016. Participants were identified from electronic databases. Only cases with confirmatory genetic testing of a deletion of *STS* by means of polymerase chain reaction (PCR), fluorescence *in situ* hybridization (FISH) or multiplex ligation probe amplification (MLPA) were included. Approval from institutional review boards were obtained.

Patient medical records were interrogated for clinical detail using a protocol-driven spread sheet. For patients with incomplete data sets, a telephone interview was carried out. Retrieved demographic data included current age, sex, and age at diagnosis. Pertinent findings on history included prenatal history; symptoms such as pruritus and hypohidrosis; and comorbidity, including atopy, cryptorchidism, neurological disease and all other comorbidity. Pruritus was defined as the presence/absence of itch in absence of any associated cutaneous findings apart from ichthyosis and was not quantified on a formal scale. Cutaneous findings included size (big, polygonal/small, round), colour (dark-brown/whitish) and location of scales, flexural involvement and palmoplantar hyperlinearity. To avoid mistaking cryptorchidism and retractile testis, and given that hormonal therapy is no longer recommended for the treatment of an undescended testis,[13] we considered cryptorchidism only in those patients who had undergone orchiopexy. Patients and caregivers were specifically asked about neurological abnormalities, including attention deficit hyperactivity disorder (ADHD), autism, cognitive impairment and epilepsy, as assessed by a neurologist colleagues. Diagnoses of ADHD, cognitive impairment and autism were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V). Patients with epilepsy demonstrated repeated unprovoked seizures occurring > 24 h apart, had electroencephalographic anomalies and were receiving (or had received) anticonvulsant therapy. Structural or metabolic causes of epilepsy had been excluded by magnetic resonance imaging and analytical assessments. Laboratory tests were performed depending on seizure type, age at onset and electroencephalography findings. A screening panel included complete blood cell count, glucose, capillary blood gas analysis, lactate [plasma and cerebrospinal fluid (CSF)], ammonia and CSF glucose. In patients with neurological abnormalities in whom DNA test results were available, a chromosomal microarray (CMA) was performed (Table S1; see Supporting Information).

Given the small sample size, descriptive analysis of normative data was the statistic investigated. Descriptive statistics are presented as mean (± SD), numerical variables as medians and categorical variables as n (%).

Results

The search found 30 patients from 25 different families. All patients were male with a median age of 15·5 years (range 0–

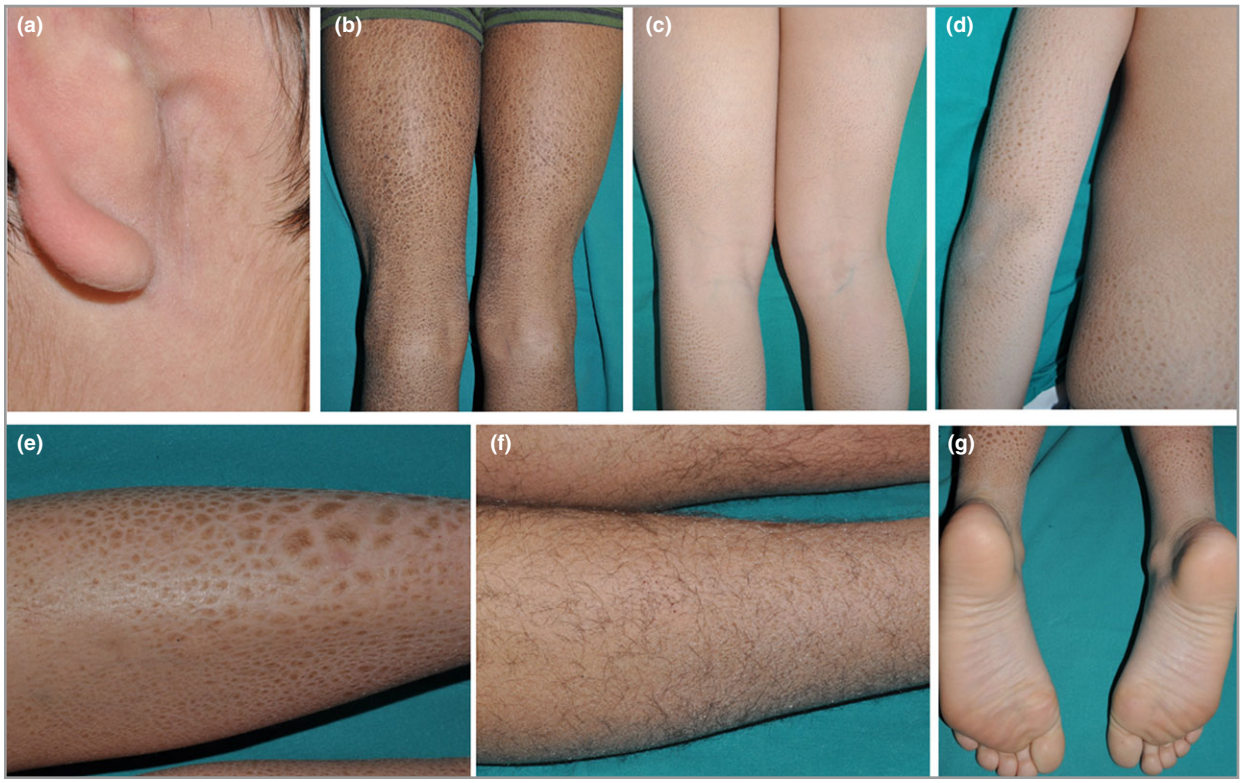

Fig 1. Clinical features in patients with X-linked ichthyosis (XLI). (a) Brown retroauricular scales giving the typical 'dirty' appearance. (b) Severe dark-brown scale on the flexor aspects of the lower legs involving the flexures. (c) Mild scaling on the flexor aspects of the lower legs lacking flexural involvement. (d) Dark-brown scales on the extensor aspects of the upper limb and trunk. (e) Typical dark-brown polygonal scales on the extensor aspects of the legs. (f) This patient, with no family history of XLI, showed mild involvement of the lower legs, making it difficult to distinguish XLI from ichthyosis vulgaris. (g) Absence of plantar hyperlinearity. Note the dark-brown desquamation on the posterior aspect of the legs. [Colour figure can be viewed at wileyonlinelibrary.com]

80). Mean age at diagnosis was 1·9 months (95% confidence interval 0·8–2·9); 13 of 28 (46%) patients were younger than 3 months, 21 of 28 (75%) were younger than 12 months and seven of 28 (25%) were older than 12 months (data not available for two patients). Orchiopexy was performed in three of 30 (10%) patients. Nine (30%) patients had been diagnosed with ADHD and four (13%) had epilepsy. Three patients had both ADHD and epilepsy. Specific data about the type of epilepsy in each patient are shown in Table 1. In addition, one patient had Tourette syndrome and another had recessive dystrophic epidermolysis bullosa (RDEB).

There was family history of XLI in 18 of the 29 (62%) patients for whom these data were available (60%). Twelve of 28 (43%) patients for whom these data were known were born by caesarean section owing to failure of progression of labour. Other demographic data and clinical findings are shown in Table 2. All individual findings are available in Table S2 (see Supporting Information).

Deletions of *STS* were assessed by PCR in 22 cases, FISH in three cases and MLPA in five cases. Two of the five patients (40%) analysed by MLPA showed an additional *HDHD1A* deletion. CMA was performed in five patients: three with both ADHD and epilepsy, and two with only ADHD. Adjacent deleted genes are shown in Table 3.

Discussion

As a whole, our case series showed clinical findings typical of XLI. At least 75% of patients were diagnosed by 1 year of age and all showed dark desquamation of variable size on the extensor surfaces of the limbs. It has been reported that a small percentage of patients with XLI display a mild phenotype consisting of xerosis and eczema,[14] similar to ichthyosis vulgaris, inhibiting clinical diagnosis, particularly in the absence of family history. Sparing of the antecubital and popliteal folds, and absence of other atopic dermatitis (AD) stigmata such as palmoplantar linearity and keratosis pilaris, have been classically advocated as useful findings to distinguish XLI from ichthyosis vulgaris.[4,15,16] However, a third of our patients (34%) showed flexural involvement, making this clinical sign poorly specific when distinguishing between the two disorders. On the contrary, the palms and soles were normal in all but one patient, and thus the absence of palmoplantar hyperlinearity seems a more reliable finding with which to make the differential diagnosis with ichthyosis vulgaris. Nevertheless, patients with XLI with palmoplantar hyperlinearity have been reported, associated or not with *FLG* mutations,[17–19] and therefore the presence of palmoplantar hyperlinearity does not exclude XLI. As we did not perform *FLG* mutation

Table 1 X-linked ichthyosis (XLI) in a retrospective series of 30 patients: specific findings in four patients with XLI and epilepsy

Patient	Age at onset	Type	Electroencephalography findings	Treatment
Patient 2	20 months	Febrile seizures at onset	Diffuse spike-and-slow-wave and polyspikes	Levetiracetam for 3 years
		Generalized-onset tonic-clonic seizures	Focal spike-and-slow-wave and sharp waves, left parietal and right temporal	
Patient 10	5 years	Generalized-onset tonic-clonic seizures	Generalized spike-and-slow-wave activity at 3 Hz	Clobazam for 6 years
Patient 12	10 months	Generalized-onset tonic and myoclonic seizures	Not known	Valproic acid for 6 years
Patient 27	12 years	Focal-onset motor clonic seizures (right arm)	Focal sharp waves, left frontotemporal and centroparietal	Levetiracetam for 2 years (ongoing treatment)

Table 2 X-linked ichthyosis (XLI) in a series of 30 patients: patient demographics and main clinical findings

Median (range) age (years)	15.5 (0–80)
Mean ± SD age (months) at onset of XLI	1.9 ± 1.02 (95% CI 0.8–2.9)
Scaling	
Size of scales	
Large	17 (57)
Small	13 (43)
Location	
Limbs	30 (100)
Scalp	23 (77)
Neck	13 (43)
Trunk	25 (83)
Flexural involvement	10 (33)
Palmoplantar hyperlinearity	1 (3)
Atopic dermatitis	7 (23)
Pruritus	18 (60)
Hypohidrosis	5/26 (19)
Extracutaneous findings	
Orchiopexy	3/10 (10)
Epilepsy	4/30 (13)
ADHD	9/30 (30)
Others[a]	2 (7)

Data are n (%) unless otherwise indicated. CI, confidence interval; ADHD, attention deficit hyperactivity disorder. [a]Tourette syndrome and recessive dystrophic epidermolysis bullosa.

analysis, we cannot draw any conclusions about such a possibility. Of note, 23% of our patients exhibited signs of AD. Similarly, an unexplained high prevalence of AD of approximately 38% was found in a series of 51 patients with XLI, regardless of the presence or absence of *FLG* mutations.[12]

Pruritus was reported by 18 of 30 (60%) patients and seems to be, as in other types of ichthyosis, a relevant complaint in XLI.[4] In contrast, hypohidrosis, a common finding in other types of ichthyosis, was uncommon, affecting only five of 26 patients (19%). To the best of our knowledge, these are the first data regarding the frequency of these findings that have been reported.

Numerous extracutaneous findings have been characteristically associated with nonsyndromic XLI, including corneal deposits that do not affect visual acuity,[20] cryptorchidism[3] and a variety of neurological disorders, including ADHD,[21] autism,[22] epilepsy and cognitive impairment.[23] As the majority of our patients were children (two of the participating hospitals were exclusively paediatric hospitals) and were not expected to have corneal deposits, our study did not incorporate routine ophthalmological examination.

Cryptorchidism, defined as the absence of at least one of the testicles in the scrotum, is the most common congenital anomaly of the male external genitalia. Its prevalence ranges from 2·4% to 9% of males born at term.[24,25] Likewise, orchiopexy rates range between 1·6% and 2·9%.[25] The aetiology of cryptorchidism remains unexplained and is likely to be multifactorial. The true association of cryptorchidism with XLI is controversial: while some authors found cryptorchidism in up to 20% of patients with XLI,[26] others found a much lower prevalence of 10%.[2] In agreement with the latter, only three of 30 (10%) of our patients underwent orchiopexy and therefore the prevalence of orchiopexy seems to be higher in patients with XLI than in the general population.

Cognitive and behavioural disorders, including ADHD (up to 40% of patients in some series),[22] autism (up to 20%),[22] epilepsy and cognitive impairment, have also been reported in patients with nonsyndromic XLI.[21,22,27–36] In our series, nine of 30 patients (30%) had ADHD and four of 30 (13%) suffered epilepsy, but none showed autism or cognitive impairment. In Spain the estimated prevalence of ADHD, a neurobiological disorder characterized by a persistent or continuous pattern of inattention and/or hyperactivity and impulsivity, is 7%,[37] a rate much lower than the 30% detected in our patients. Although studies in mice support the theory that genetic deletion of *STS* may include regions critical to the development of behaviour,[38] ADHD has also been described in patients with XLI with small, partial deletions or even point mutations of *STS*,[22] favouring the theory that it would be the STS deficiency in itself rather than the length of the genetic anomaly that would cause behavioural disturbances.[39–41] There are several facts supporting this statement: firstly, behavioural anomalies have been demonstrated in mice with *STS* haploinsufficiency (39X0);[39] secondly, STS converts the sulfated form of dehydroepiandrosterone (DHEAS) into DHEA

Table 3 Chromosomal microarray performed in five patients, three showing both epilepsy and attention deficit hyperactivity disorder (ADHD) and two with ADHD exclusively

	Type	Chromosome	Cytoregions	Size (kbp)	OMIM® genes
Epilepsy and ADHD					
Patient 12	Loss	X	p22.31	1 684 379	*HDHD1*, *MIR4767*, *STS*, *VCX*, *PNPLA4*, *MIR651*, *VCX2*
Patient 27	Loss	X	p22.31	1 679 614	*HDHD1* (306480), *STS* (300747), *VCX* (300229), *PNPLA4* (300102)
Patient 2			p22.31	Unknown	*HDHD1* (306480), *STS* (300747), *VCX* (300229), *PNPLA4* (300102)
ADHD only					
Patient 20	Loss	X	p22.31	1 680 417	*HDHD1* (306480), *STS* (300747), *VCX* (300229), *PNPLA4* (300102)
Patient 22	Loss	X	p22.31	1 357 684	*HDHD1* (306480), *STS* (300747), *VCX* (300229), *PNPLA4* (300102)

(both substances are steroids with effects on neuropsychological and behavioural processes);[40] and, thirdly, a 3-month treatment course of methylphenidate produced significant clinical improvement in boys with ADHD and increases in serum concentrations of DHEAS and DHEA, suggesting that these neurosteroids may play a role in the therapeutic effects of methylphenidate.[41]

The prevalence of epilepsy in developed countries ranges from 0·4% to 1%,[42] a much lower rate than the 13% documented in our series of patients. Electroencephalography anomalies and epilepsy, along with *STS* deletions, have rarely been reported in the literature, either in association with cognitive impairment,[28,32] structural brain anomalies,[27,30] or without accompanying mental delay or any neuroimaging finding.[29] A possible explanation of the low reported frequency in previous studies is that epilepsy (even when requiring long-term anticonvulsant therapy) seems to abate during childhood, and patients often omit this once it is no longer an active issue. Moreover, for most patients this condition and cutaneous (and usually mild) desquamation are not thought to be related. The origin of epilepsy in patients with XLI is uncertain; some authors believe that it might be caused by a loss of genetic material adjacent to *STS*,[27] whereas others suggest that prolonged labour can cause cerebral ischaemia and secondary epileptic foci.[43] In accordance with the first theory, it is worth mentioning that, to date, epilepsy has only been reported in patients showing *STS* deletions,[23,27–30,32] as in our four cases. Nevertheless, unlike prior reported cases, none of our patients presented any other symptoms, suggesting a large deletion of *STS*, and therefore the deletion size does not seem to be crucial. Also, although three of our patients had prolonged labour and two of them required caesarean section, one had a normal, nonprolonged delivery and therefore epilepsy cannot be explained by perinatal hypoxia due to prolonged labour.

Another intriguing finding is that three of our four patients with epilepsy also had ADHD. Patients with similar findings have been reported twice,[27,29] but there were no further comments regarding the coincidence. It has been claimed that a number of genes adjacent to *STS*, such as *Nlg4*,[44,45] *VCX3A*[34] and *PNPLA4*,[23] are responsible for autism and cognitive impairment, but studies have consistently failed to find this.[46,47] CMA performed in two patients with ADHD and epilepsy and two with ADHD showed deletions in *PUDP* (306480), *VCX* (300229) and *PNPLA4* (300102), excluding a strong causal relationship between the absence of these genes and intellectual disability and/or autism and phenotype variations in ADHD and epilepsy. Whether other genes [small microRNAs (miR) miR4767 and miR651] found to be deleted in the third patient with ADHD and epilepsy are involved in his neurological issues is uncertain. However, Xp22·31 duplications involving *STS* have been associated with cognitive deficits, seizures and talipes.[48–50] Although in all cases the patients showed maternal chromosome X amplification, such an amplification has been also reported in healthy people. A genomic dosage model has been proposed to explain differences in the manifestations of several diseases. Therefore, it is possible that *STS* deletion could be associated with other gene abnormalities that would explain the phenotypic variability.

Large deletions of *STS* may include additional genes causing the so-called contiguity syndromes. None of our patients had any clinical findings suggestive of a contiguity syndrome [i.e. cognitive impairment, short stature, recessive form of chondrodysplasia punctata, Kallman syndrome (anosmia and hypogonadotropic hypogonadism)],[3] which have been reported in up to 8% of patients diagnosed prenatally as STS deficient.[51] However, one patient was diagnosed with Tourette syndrome and another (previously reported in the literature)[52] had RDEB. While the genetic background of Tourette syndrome is uncertain, the genetic basis of RDEB is well known,[52,53] and its association with XLI seems to be coincidental, as in other conditions (Table 4).[54–62]

The importance of potential obstetric complications in XLI female carriers deserves a final comment. In the placenta, STS participates in the oestrogen synthesis pathway by

Table 4 Reported associations with nonsyndromic X-linked ichthyosis

Neurofibromatosis type 1[54]
Primary microcephaly secondary to *ASPM* mutation[55]
Léri–Weill dyschondrosteosis[56]
Crigler-Najjar syndrome[57]
Pyloric hypertrophy[58]
Testicular cancer[59]
Nephrotic syndrome and renal agenesis[60]
Acute lymphoblastic leukaemia[65]
Congenital defect of the abdominal wall[61]
Poland syndrome[62]

deconjugating DHEAS.[63] Insufficient levels of oestrogen impair dilation of the cervix and decrease response to oxytocin stimulation, which often leads to prolonged labour, the need for caesarean section in female carriers, and therefore an increased risk of obstetric complications.[43,64] In our series, 12 of 28 (43%) of our patients' mothers required caesarean sections because of failure to progress in labour. Dermatologists should be aware of this possibility in women with a family history of XLI to give them and their gynaecologists the appropriate counselling in order to mitigate prenatal obstetric complications.

Our study has some limitations. This was a retrospective study based primarily on review of patient medical records, supplemented by telephone interviews, and therefore omission of some clinical information and recall bias are possible. Additionally, our case series was relatively small and only patients with a genetic deletion of *STS* were included.

Dark-brown scaling on the extensor surfaces of the extremities is a consistent finding in patients with XLI. The absence of palmoplantar hyperlinearity seems to be the most reliable finding when differentiating XLI from ichthyosis vulgaris. The prevalence of orchiopexy is higher than in the general population, and dermatologists should be aware that the prevalence of ADHD and epilepsy is considerably higher in patients with XLI than in the general population.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Chromosomal microarray methodology.

Table S2 Demographic, clinical and molecular data of all 30 patients.