X-linked ichthyosis: an update

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Summary

X-linked ichthyosis is a genetic disorder of keratinization characterized by a generalized desquamation of large, adherent, dark brown scales. Extracutaneous manifestations include corneal opacity and cryptorchidism. Since 1978 it has been known that a deficit in steroid sulphatase enzyme (STS) is responsible for the abnormal cutaneous scaling, although the exact physiological mechanism remains uncertain. The STS gene has been mapped to the distal part of the short arm of the X chromosome. Interestingly, this region escapes X chromosome inactivation and has the highest ratio of chromosomal deletions among all genetic disorders, complete deletions having been found in up to 90% of patients. Diagnosis of patients with X-linked ichthyosis and female carriers is based on biochemical and genetic analysis. The latter currently seems to be the most accurate method in the majority of cases.

Key words: gene deletion, ichthyosis, steroid sulphatase, X-linked ichthyosis.

Epidemiology

X-linked ichthyosis is a relatively common genetic disorder, affecting approximately 1 in 6000 males,14,15 with no significant racial or geographical differences. As seen in all diseases with a sex-linked recessive hereditary trait, X-linked ichthyosis is transmitted by women and affects males almost exclusively. Very few cases of women having the disease have been reported to date; such is the case of three homozygous women, daughters of a male with the disease and a female carrier of X-linked ichthyosis.16

Clinical features

Cutaneous manifestations

X-linked ichthyosis is characterized by the presence of dark brown, polygonal scales on different parts of the body surface. The lesions are usually distributed...
symmetrically and are generally more evident on the extensor aspects of the limbs, particularly on the lower extremities. Scale size varies individually but in general the scales are larger on the extensor areas of the lower limbs than on the upper part of the trunk. The face is usually free of scales, except in the preauricular areas, which according to some authors is a pathognomonic feature. Often, but not always, the flexures are affected (Fig. 1), as are the neck and scalp, where pityriasiform desquamation is observed. The palms and soles are very rarely involved, although such involvement does not exclude a diagnosis of X-linked ichthyosis. The hair and nails are normal.

Unlike ichthyosis vulgaris, X-linked ichthyosis appears very early on in life. The disease presents with a generalized desquamation of large, slightly adherent, light colored scales that are replaced over the following weeks by polygonal dark scales strongly adherent to the skin surface. During early childhood, the scalp is almost always affected and, often, so are the preauricular areas, the lateral parts and back of the neck, which has a ‘dirty’ appearance owing to the brown colour of the scales (Fig. 2). With time, lesions on the head almost completely disappear, while those on the trunk and limbs, especially on the extensor surfaces of the lower limbs, become more prominent. Although the disease persists throughout the patient’s life, desquamation improves during the summer and becomes worse during dry and cold weather.

Extracutaneous manifestations

Ocular alterations. Corneal opacity is undoubtedly the most characteristic ophthalmological abnormality found in X-linked ichthyosis. It is estimated that between 10 and 15% of affected males and female carriers have diffuse corneal deposits in the posterior capsule of Descemet’s membrane or corneal stroma. Although these lesions may appear at any time in the patient’s life, some authors have found them to be more frequent during the second and third decades of life. Nevertheless, they never affect visual acuity. Additionally, posterior embryotoxon, deuteranopsia, and one case of recurrent corneal erosion in a patient with X-linked ichthyosis and simple bullous epidermolysis, possibly secondary to the rubbing produced by palpebral hyperkeratosis, have been reported.

Gonadal alterations. The incidence of cryptorchidism is higher in patients with X-linked ichthyosis than that expected in the general population, suggesting that this anomaly could also be due to the deficit in STS or perhaps to a genetic disturbance located on the short arm of chromosome X close to the STS gene. Several cases of testicular cancer and of secondary hypogonadism without associated cryptorchidism have been reported, although the exact role of STS in testicular differentiation remains to be elucidated.

Central nervous system alterations. Among the neurological findings observed in patients with X-linked ichthyosis are electroencephalographic findings attributable to the slowing of delivery secondary to a placental deficit in STS, epileptic seizures and reactive psychological disorders.

Other alterations. Two cases of patients with X-linked ichthyosis suffering from pyloric hypertrophy have been reported. Accordingly, some authors have suggested that the aetiology of the hypertrophic pyloric
stenosis could be due to a chromosome X-linked recessive gene that would occupy a locus close to that of X-linked ichthyosis.\textsuperscript{35} One case of a patient with X-linked ichthyosis and acute lymphoblastic leukaemia has also been reported\textsuperscript{37} as well as a case with an associated congenital defect of the abdominal wall.\textsuperscript{38}

**Pathology and cell kinetics**

Histological studies show compact, eosinophilic hyperkeratosis, occasionally parakeratotic, under which the stratum granulosum appears normal or slightly thickened.\textsuperscript{25,39} Most authors have not observed follicular hyperkeratosis while, for others, this is prominent.\textsuperscript{25,40} The dermis displays oedema and a slight perivascular inflammatory infiltrate. The cutaneous adnexae are normal.\textsuperscript{25}

Ultrastructural analysis reveals an increase in the number and volume of keratohyalin granules, while the keratinocytes appear normal.\textsuperscript{41,42} The keratinocytes appear linked by desmosomal discs up to the most superficial layers of the epidermis, pointing to increased intercellular cohesivity. Corneal cells also contain large numbers of melanosomes, probably due to a decrease in their spontaneous degradation. This would explain the dark colour of the scales.\textsuperscript{41}

Unlike other ichthyoses, studies on cell kinetics using tritiated thymidine demonstrate a normal rate of cell replacement in patients with X-linked ichthyosis.\textsuperscript{39} Finally, it has been observed that in X-linked ichthyosis transepidermal water loss is not impaired, and that skin reactivity in such patients was decreased when irritants such sodium lauryl sulphate were patch tested.\textsuperscript{43}

**The steroid sulphatase enzyme**

The sulphatases are a group of enzymes that catalyse the reaction:

\[
\text{ROSO}_3\text{H} + \text{H}_2\text{O} \rightarrow \text{ROH} + \text{H}^+ + \text{HOSO}_3^- 
\]

STS (sterol sulphate sulphotydrase, EC 3.1.6.2) is an insoluble hydrolytic enzyme bound to the microsomal membrane, with a molecular weight of 62 kDa and able to cleave the sulphate groups of the 3β position of sterols and steroids. Its best known natural substrates are dihydroepiandrosterone sulphate (DHEAS) and cholesterol sulphate, although the enzyme is also known to hydrolyse other steroid sulphates, such as pregnenolone sulphate and androstenediol-3-sulphate.\textsuperscript{44} It is widely distributed throughout human and foetal tissues and, among other sites, STS activity has been detected in brain, liver, adrenal cortex,\textsuperscript{45} placenta,\textsuperscript{5} skin,\textsuperscript{1,2} testicles,\textsuperscript{46} ovary\textsuperscript{47} and leucocytes.\textsuperscript{8,10,11}

The arylsulphatases form a group of enzymes that catalyse the hydrolysis of different sulphated aromatic esters. In human tissues, there are at least five types of arylsulphatases: arylsulphatase A–E. The activity of the arylsulphatase C can only be determined in vitro by using artificial substrates such as paranitrocatechol sulphate, paranitrophensulphate, 6-bromo-2-naphthyl sulphate or 4-methyl-umbelliferyl sulphate.\textsuperscript{44} Several authors have reported a simultaneous deficit of STS and arylsulphatase C in patients with X-linked ichthyosis,\textsuperscript{1,2,9,48} and some of them have proposed that both STS and arylsulphatase C could be isoenzymes.\textsuperscript{48,49} Evidence against this hypothesis derives from the fact that in hair follicles hydrolytic activity only occurs for the particular substrate of arylsulphatase C, 4-methyl-umbelliferyl sulphate, whereas DHEAS remains sulphated.\textsuperscript{50} Currently, arylsulphatase C is believed to have two isoenzymes, one of which is identical to STS.\textsuperscript{51,52}

**Function of the steroid sulphatase enzyme**

*Placenta.* The placenta, an STS-rich tissue of embryonic origin, is responsible for deconjugating DHEAS, produced both by the mother and the foetal adrenal glands, as a step before oestrogen synthesis. In the presence of normal foetal growth and development, DHEAS crosses the placenta, is deconjugated by STS, and is then converted into oestrone or oestradiol through a series of enzymatic reactions (Fig. 3).\textsuperscript{53} Following this, part of these two compounds returns to the foetal tissues and is converted into oestriol, which in quantitative terms is the most important oestrogen during pregnancy. In pregnancies in which STS is deficient, a metabolic blockade occurs that leads to an overall decrease in the levels of oestrogen, the final reaction product.

To date, all pregnancies studied with STS deficiency have been of male foetuses.\textsuperscript{21,53} The enzyme deficiency causes a slowing of delivery because of insufficient dilatation of the cervix, with a relative failure of response to intravenous oxytocin.\textsuperscript{21,53,54} Both are indications for caesarean section or instrumental delivery and hence there is an increase in perinatal morbidity and mortality.

*Epidermis.* Lipids are a major component of skin and form approximately 11% of the dry weight of the
epidermis. Of such lipids, about 10% are sterols, among which cholesterol sulphate is included, forming 5% of the total lipids of the granular layer and rather less in the stratum corneum and lower layers of the epidermis. Cholesterol sulphate is found in greater proportions in the lower zone of the stratum corneum than in the more superficial layers and hence a relationship is believed to exist between the gradient of cholesterol sulphate through the stratum corneum and normal cutaneous desquamation. It is believed that the higher relative proportion of cholesterol sulphate may alter the physical properties of the cell membranes of the stratum corneum, increasing their stability and the degree of intercellular cohesion. It is also known that cholesterol sulphate inhibits cholesterol synthesis, both in normal fibroblasts and in the fibroblasts of patients with X-linked ichthyosis. As the stratum granulosum is an active site of cholesterol production, the cholesterol sulphate of the lower stratum corneum would be able to regulate the steroidogenesis of the adjacent strata through a feedback mechanism. As a result, through cholesterol sulphate, STS could indirectly control steroid production in the granular layer of the epidermis.

On the other hand, the concentration of sulphated steroids seems to play a crucial part in the process of capacitation of spermatozoa through the inhibition of a protease called acrosin. Consequently, if epidermal cholesterol sulphate is also able to inhibit the proteases of the membranes of the stratum corneum (carboxypeptidase, cathepsin B, etc.), a rise in its concentration would prevent the degradation of desmosome structures in the most superficial corneocytes, increasing intercellular cohesion and preventing normal desquamation. In summary, although the identification of STS as a cause of X-linked ichthyosis points to the important role of this enzyme in skin desquamation, the exact physiological mechanisms regulating this remain to be elucidated.

The steroid sulphatase enzyme gene

The gene encoding STS has been mapped to the distal part of the short arm of the X chromosome (Xp22.3-pter). This zone is of special interest for several reasons: (i) it escapes X chromosome inactivation (Lyon’s theory); (ii) it shares important sequence homologies with the Y chromosome; and (iii) it is an area in which deletions occur more frequently than normal.

According to Lyon’s theory, inactivation of one of the two X chromosomes in women ensures a balance between the genetic load of the two sexes. The STS enzyme escapes this inactivation at least in part and, in normal individuals, enzymatic activity in women is greater than in men. The proportion of STS between sexes is approximately 1.6 and not 1.0, as would be expected if ‘lyonization’ were total; therefore, inactivation is believed to be only partial.

The existence of two dimorphic sexual chromosomes poses a second problem: the need for them to pair during male meiosis so that segregation into gametes can occur. This is achieved through the maintenance of a region with sequence identity on both chromosomes, the pseudoautosomal region. Accordingly, the genes located in the pseudoautosomal region do not
require the above genetic compensation because they are present on both the X and Y chromosomes. The STS gene is located close to the pseudoautosomal region, but not in it, and hence the fact that it escapes inactivation is quite remarkable.

The explanation for the high frequency of chromosomal deletions in this region of the X chromosome seems to be an unequal crossing over during the female meiosis. Direct support for such a mechanism at the STS locus has been provided recently by an analysis of a hypervariable locus (called CRI-232) flanking the gene. Thus, the repetition of CRI-232 sequences across STS may be responsible for mispairing at meiosis and unequal recombination leading to deletion.

The STS gene consists of 10 exons and spans over 146 kb of DNA. The size of the non-coding sequences, or introns, that separate the exons varies considerably, ranging between 102 bp (intron 3) and 35 kb (intron 1). By contrast, nearly all the exons are between 120 and 160 bp long. In all intron–exon junctions there is a GT-AG sequence and, with the exception of intron 9, the amino acid encoded at the splice donor site is an arginine or a glycine. The importance of this observation remains to be clarified. The Y chromosome does not have a functional STS gene, although a pseudogene of 100 kb is known to exist on the long arm of the Y chromosome.

Ballabio et al. analysed the STS gene using both Southern blot and polymerase chain reaction (PCR) techniques, finding that in X-STS only exons 1, 5 and 10 had unique nucleotide sequences. As a result, Southern blot hybridization with a complete STS cDNA probe detects fragments from both chromosome X and chromosome Y, with the exception of those fragments that contain exons 1, 5 and 10, which appear exclusively in the X chromosome. For this reason, Southern blot studies to detect STS gene deletions in males must be performed exclusively with cDNA containing exons 1, 5 and 10.

The STS gene is transcribed into mRNA and then translated into a protein of 561 residues with enzymatic activity. Northern blot analyses of RNA reveal that the size of the transcription fragments varies as a function of the tissue from which the RNA has been extracted and that different types of RNA may exist in the same tissue. Thus, whereas in placenta there are two major RNA transcripts of 2·7 and 5·2 kb each, in fibroblasts they are 5·2 and 7·2 kb long, respectively. Some authors have suggested that the different lengths of the transcribed sequences is due to the existence of different polyadenylation sites, and not to alternative splicing.

The DNA sequence of nucleotides corresponding to the 2·7 kb RNA segment has been determined, using the dideoxy chain termination method. The cDNA of STS contains an untranslated 5’ end of at least 206 bp followed by an open-reading frame (coding sequence) of 1542 bp, while the 3’ end has 668 bp, at the end of which there is a polyadenylation signal, 13 bp before the true polyadenylation region. The sequence of the 23 initial amino acids of the N-terminal end of the STS protein has also been determined; the first 22 contain mainly hydrophobic residues, possibly corresponding to a signal peptide that is cleaved after translation to yield the definitive or mature STS protein. Three hypothetical N-glycosylation sites with the Asn-X-Thr residues have been proposed at codons 25, 237 and 311 as well as a 16 amino acid sequence close to the C-terminal end (residues 437–452), very rich in serine and threonine, susceptible to O-glycosylation. Finally, the hydrophobic regions detected along the amino acid sequence, located especially between residues 160 and 220, are thought to serve as an anchor point for the microsomal membrane.

Steroid sulphatase enzyme gene deletions

Ninety per cent of patients with X-linked ichthyosis show a complete deletion of the STS gene, meaning that X-linked ichthyosis is the genetic defect with the greatest incidence of complete deletions. The other cases display only partial deletions (Table 1) or point mutations in the nucleotide sequence that destroy the enzymatic activity of the protein.

The magnitude of the deletion of the STS locus varies from subject to subject. Using flow cytometry, Cooke et al. were able to detect deletions in some but not all patients with deficits in STS, and estimated the size of the deleted fragment, when present, at between 1·2 and 3·4% of the total length of the X chromosome, equivalent to 1·9–2·5 million bp. This measurement would represent the upper limit of deletion size of the STS locus in individuals in which X-linked ichthyosis is the only phenotypical defect, whereas the lower limit can be estimated at 150–800 kb in length and cannot be detected by flow cytometry. It seems that, in most cases, the size of deletions is of 2 Mb. Interestingly, most deletions include the DXS278 marker, but the fact that the patients are clinically indistinguishable from patients with point mutations of the gene suggests that this adjacent genetic material is not functional. Very few cases of partial deletions of the STS gene have been
reported to date. One of the patients had an intragenic deletion of 45 kb located between introns 1 and 5, another had a deletion of 150 kb at the 5′ end of the gene and three more had a deletion at the 3′ end. Some patients with complete absence of STS enzymatic activity do not show alterations in the STS gene when their DNA is hybridized with STS cDNA. These cases correspond to point mutations in the nucleotide sequence that elicit an amino acid change in the final STS protein with functional repercussions. Until now, substitution of tryptophan by arginine, serine by leucine, and cysteine by tyrosine has been reported in three different patients, as well as a point mutation in exon 7 in which glycine became a stop codon, a switch of tryptophan to proline, and a change of histidine to arginine and a 19-bp insertion starting at nucleotide 1477 (Table 2). All patients have a unique single base pair substitution on the genomic level. The close proximity of the mutations within 105 residues in the C-terminal half of the STS polypeptide suggests that this region (the 3′ end of the gene) is important to the structure or function of the STS enzyme. However, some partial deletions have been found at the 5′ end or between introns 1 and 5 of the gene. In 1995 a patient with X-linked ichthyosis was described in whom it was not possible to detect either biochemical or genetic alterations at STS level; it was proposed that the disease might also be due to alterations at other points of the genome, not genetically linked to the STS gene.

### Syndromes of genetic continuity

Karyotypically normal subjects showing a deficit in STS can be classified in two different groups: those with X-linked ichthyosis as the only clinical manifestation, and those showing other associated phenotypical anomalies, probably due to broader chromosomal deletions.

Study of the interstitial and distal deletions of the Xp22.3-pter region has allowed the assignment of several genes, apart from STS, to this region: the gene of the Xg blood group, the MIC2 gene, the chondrodysplasia punctata gene, the gene for Kallmann’s syndrome, the short stature gene and a gene whose deletion results in moderate mental retardation (Fig. 4).

### Short stature

Although both genetic and environmental factors are involved in stature, a locus is believed to be present on the distal region of Xp whose deletion determines short stature in affected males and heterozygous females. For some authors, this gene could be located within the pseudoautosomal region, distal to the locus of the MIC2 gene.

### Chondrodysplasia punctata

Chondrodysplasia punctata is a congenital disorder characterized by abnormalities in cartilage and bone development. There are two types of X-linked chondrodysplasia punctata due to abnormalities in a gene located at the Xp22.3,pt region: a dominant rhizomelic form that is lethal in males, and a milder recessive form. The description of two families with an interstitial chromosomal deletion in which X-linked ichthyosis was associated with Kallmann’s syndrome suggests

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that the gene for chondrodysplasia punctata is located distally to both genes. The gene responsible for chondrodysplasia punctata, named ARSE, has been cloned recently, and it is known to belong to the arylsulphatase gene family (arylsulphatase E).

Mental retardation

The distal deletions that include the STS gene and the marker DSX32, located distally with respect to the STS gene, are always accompanied by a moderate degree of mental retardation (IQ 50–70) and a gene responsible for mental retardation has been located nearby. However, the exact characterization of this gene is hindered because different genes are involved in normal mental development and have been described in patients with ichthyosis X, while patients with mental retardation have been described in which the genetic deletion did not include the DSX32 gene.

Kallmann’s syndrome

The locus of Kallmann’s syndrome, a disease characterized clinically by hypogonadotropic hypogonadism and anosmia, has been mapped proximal to the STS gene for two reasons: the observation of three families in which Kallmann’s syndrome cosegregates with X-linked ichthyosis in the absence of other manifestations attributable to the deletion of distal genes and the absence of symptoms of Kallmann’s syndrome in patients with X-linked ichthyosis carrying terminal deletions on the short arm of chromosome X. Recently, a gene of 820 kb has been reported at this location; it encodes a substance similar to the neural cell adhesion molecule (NCAM-like) and its mutation could be responsible for Kallmann’s syndrome.

Laboratory diagnosis of X-linked ichthyosis

Biochemical diagnosis

Biochemical diagnosis of X-linked ichthyosis consists of demonstrating STS deficiency in whichever tissue the enzyme exists, either by demonstrating the lack of enzymatic activity (direct biochemical assays) or by determining an increase in one of its substrates. Direct biochemical techniques demonstrate either STS or arylsulphatase C deficiency in one of the places where it is usually found: placenta, skin fibroblasts, leucocytes and keratinocytes. The substrate, linked to a radioactive marker, is incubated with an STS-rich tissue. Then either the hydrolysed or the non-hydrolysed substrate is measured as a function of the residual radioactive activity. STS substrates are DHEAS (the most frequently used), cholesterol sulphate, as well as oestrone sulphate and vitamin D₃ sulphate. Arylsulphatase C requires an artificial substrate, 4-methylumbelliferyl sulphate. Histochemical assays can be used to assess arylsulphatase C activity in skin and placental tissue, by adding 6-bromo-2-naphthylsulphate as a substrate. Indirect tests demonstrate the presence of cholesterol sulphate or DHEAS substrates where they are secreted or deposited. The lack of cholesterol sulphate hydrolysis elicits a significant increase in this substance both in the stratum corneum and in serum. In serum, cholesterol sulphate, which is negatively charged, is carried by some lipoprotein fractions, altering their electrophoretic mobility. Consequently, electrophoresis of lipoproteins in patients with ichthyosis X reveals an increase in the migration speed of these particles towards the positive pole. The technique is simple and rapid but may give false negatives, as has been found in some individuals with X-linked ichthyosis who have normal electrophoretic mobility. More recently, new methods have been designed to demonstrate increases in cholesterol sulphate in serum, such as chromatography or spectrophotometry. In the stratum corneum, the increase in cholesterol sulphate can be detected by lipid thin-layer chromatography.
Genetic diagnosis

The most recent diagnostic methods are based on direct analysis of genetic material. The use of laboratory techniques such as Southern blot, in situ hybridization and PCR has allowed the molecular detection and study of STS gene deletions. Genetic tests yield reliable results in most affected patients. Only a very small number of cases, carrying point mutations instead of deletions at the STS gene, are undetectable by Southern blot or PCR.

Prenatal diagnosis

Different procedures can be used in prenatal diagnosis, such as amniocentesis or foetoscopy for foetal skin biopsy. However, non-invasive techniques based on maternal serum analyses are preferred to avoid risks to the foetus.

The deficit in placental STS blocks the synthesis of placental steroids which, as a result, are excreted in much lower amounts in the urine of the pregnant woman. As other foetal pathologies, such as adrenal insufficiency, anencephaly or Down syndrome, may also present with decreased urinary placental oestrogen excretion, the detection of non-hydrolysed, sulphated steroids in the urine of pregnant women would be preferable.

Among the invasive methods used to confirm deficiencies in STS are the culture and analysis of fibroblasts obtained from amniotic fluid and the determination of CS levels in amniotic fluid and cord plasma.

Finally, the above-mentioned genetic techniques would be also useful to obtain a prenatal diagnosis of X-linked ichthyosis in foetal tissues.

Diagnosis of female carriers

In X chromosome-linked recessive inheritance, all the daughters of affected males are carriers and do not require confirmation by analysis. However, only half the daughters of these daughters are carriers, so that it is useful to determine which are heterozygous.

Owing to partial inactivation of the X chromosome, the fibroblasts and leucocytes from healthy women show greater STS enzymatic activity than in heterozygous women. The STS value in the latter is generally similar to that of normal males, although there are cases in which the STS activities of heterozygous and normal women tend to overlap. Accordingly, these measurements are not completely reliable.

Indirect biochemical tests are also unable to give fully satisfactory results as regards the detection of carriers. Thus, whereas electrophoresis of β-lipoproteins carried out over 30 min is diagnostic in most males with X-linked ichthyosis, it is not so in female carriers. Although some authors have reported increased electrophoretic lipoprotein mobility in female carriers when electrophoresis is continued for 50 min, the shift is not as clear as in affected males and the results are insufficiently confirmed.

The genetic methods of diagnosis have also brought a considerable improvement in the detection of carriers, although they have not yet been fully developed. Some authors report satisfactory results on comparing the differences between the genetic load of affected subjects, heterozygotic carriers and normal women by Southern blot and densitometry. Others have successfully used in situ hybridization for the diagnosis of carriers and PCR with high-performance liquid chromatography. The results, however, remain to be fully confirmed.

Treatment

All treatments of ichthyosis attempt to diminish the abnormal keratinization by facilitating the elimination of scales or preventing their reproduction. Fortunately, most cases of X-linked ichthyosis improve spontaneously with age and during the summer and hardly require any treatment.

The milder forms benefit from topical keratolytics, emollients, and hydrating agents. Topical isotretinoin may also improve the condition. Although patients severely affected with ichthyosis nigrans are exceedingly rare, oral retinoids are a potential treatment in such patients.

Also a recent study suggested that liarozole, a new imidazole derivative able to inhibit cytochrome P450, may be of use in disturbances of keratinization, such as in X-linked ichthyosis and laminar ichthyosis, because it increases the level of endogenous retinoic acid by blocking its P450-dependent catabolism.

Fortunately, severely affected individuals are rarely seen. Many of these patients would be glad of a safe effective treatment, at least during adolescence and young adult life, at a time when the unusual appearance of the skin can be a significant handicap both socially and at work. Patients in this age range generally tolerate side-effects of treatment well if they can perceive some cosmetic benefit. However, the more effective treatments now available are still symptomatic rather than curative. They may be expensive and have troublesome side-effects. Increased understanding of
the genetic and pathological processes will lead to better and more widely available genetic counselling while technical advances will allow improved prenatal diagnosis and diagnosis of female carriers.

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