

REVIEW ARTICLE

X-linked ichthyosis: New insights into a multi-system disorder

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Abstract

Background: X-linked ichthyosis (XLI) is a rare genetic condition almost exclusively affecting males; it is characterised by abnormal desquamation and retention hyperkeratosis, and presents with polygonal brown scales. Most cases result from genetic deletions within Xp22.31 spanning the STS (steroid sulfatase) gene, with the remaining cases resulting from STS-specific mutations. For many years it has been recognised that individuals with XLI are at increased risk of cryptorchidism and corneal opacities.

Methods: We discuss emerging evidence that such individuals are also more likely to be affected by a range of neurodevelopmental and psychiatric traits, by cardiac arrhythmias, and by rare fibrotic and bleeding-related conditions. We consider candidate mechanisms that may confer elevated likelihood of these individual conditions, and propose a novel common biological risk pathway.

Results: Understanding the prevalence, nature and co-occurrence of comorbidities associated with XLI is critical for ensuring early identification of symptoms and for providing the most effective genetic counselling and multidisciplinary care for affected individuals.

Conclusion: Future work in males with XLI, and in new preclinical and cellular model systems, should further clarify underlying pathophysiological mechanisms amenable to therapeutic intervention.

1 | X-LINKED ICHTHYOSIS

The ichthyoses are dermatological conditions arising from abnormal cornification and desquamation processes, and characterised by dry, thickened scales.¹ In the early 20th Century, an ichthyosis subtype inherited as an X-linked recessive trait (i.e., transmitted from unaffected female carriers to sons) was identified.² Biochemical studies in skin fibroblasts of affected individuals correctly predicted deficiency for the enzyme steroid sulfatase (STS) as a causal mechanism,³ and the STS gene was subsequently cloned.⁴ STS cleaves sulfate groups from multiple steroid hormones (e.g.,

dehydroepiandrosterone sulfate, DHEAS), affecting their water-solubility, bioavailability, and activity.⁵ The central mechanism behind the skin phenotype in 'X-linked recessive ichthyosis' (XLI) is probably an accumulation of cholesterol sulfate (and a deficit of cholesterol) in the stratum corneum.^{6,7}

Clinically, XLI presents from birth (or shortly afterwards) with widely-distributed polygonal, translucent scales which are gradually replaced with large, darker brown-grey scales occurring primarily on the neck, trunk, and lower extremities, and on extensor surfaces.⁸ Most affected males inherit an Xp22.31 genetic deletion from a heterozygous carrier mother; this can be STS-

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specific, but is typically 1.5–1.7Mb in size, encompassing *STS* and its immediate neighbours (the protein-coding genes *PUDP(HDHD1)*, *VCX*, and *PNPLA4* and the non-coding microRNA *MIR4767*).^{8–11} In the remaining XLI cases, the causal variant is an *STS* point mutation or, rarely, a larger deletion covering many contiguous genes.^{8–11} Individuals with extensive deletions frequently present with multiple developmental issues ('syndromal ichthyosis')¹⁰; here, we largely focus on typical 'non-syndromic' XLI cases.

Prenatal screening studies estimate typical Xp22.31 deletions to be present in 1 in 1500 general population males,^{12,13} yet XLI is diagnosed in as few as 1 in 6000 males.⁸ This implies *STS* deficiency is associated with a spectrum of skin disease, with many carriers either not receiving an XLI diagnosis, or being misdiagnosed. Consistent with this, individuals ascertained genetically present with less severe skin phenotypes than those ascertained in dermatology clinics.¹⁴ Moreover, <60% of phenotypically-characterised males with Xp22.31 deletions <10Mb around *STS* reported in the DECIPHER clinical genetics database (the 'DECIPHER XLI-relevant cohort') are identified as having ichthyosis or a 'skin abnormality'.¹⁵ The severity of the skin condition in XLI may be modified by an individual's background genetics, notably variants within the autosomal *FLG* (filaggrin) gene.¹⁶

As Xp22.31 gene products are widely-expressed in the human body,¹⁷ their deficiency may be associated with extracutaneous medical phenotypes. Recognition of such phenotypes has been hampered by the rarity of XLI, superfluous phenotyping of cases, and ascertainment biases (cases have largely been identified in dermatology clinics on the basis of their moderate-severe skin condition, and are often young). Over the past decade, improved recruitment across the age range, genotyping/phenotyping and data collation and dissemination strategies (particularly through large-scale biobanks and clinical genetics resources), has revealed new genotype-phenotype associations.

2 | ESTABLISHED MEDICAL COMORBIDITIES

2.1 | Cryptorchidism

Case reports/series published in the late 1970s and early 1980s highlighted a putative association between XLI and bilateral or unilateral cryptorchidism (testicular maldescent into the scrotum during development)¹⁸; these early studies indicated cryptorchidism in 10%–40% of individuals with XLI, notably in those whose birth was beset by obstetric complications (placental *STS* deficiency delays or prolongs labour in >60% of carrier mothers¹⁹). More recent case series,^{20,21} and the DECIPHER XLI-relevant cohort,¹⁵ suggest a

What's already known about this topic?

- X-linked ichthyosis (XLI) has long been associated with an increased risk of testicular maldescent and corneal opacities.
- Historic use of comparatively small samples of young participants has limited our ability to detect comorbidities of medical significance.

What does this study add?

- Recent larger-scale studies including older participants have uncovered new clinically-significant medical conditions associated with XLI, and point to common pathophysiological mechanisms.
- Understanding the prevalence and nature of conditions associated with XLI will ensure optimal genetic counselling and multidisciplinary care for affected individuals, and will signpost new research avenues in patients and model systems.

cryptorchidism prevalence rate in XLI of around 10%–15%, consistent with the lower end of this initially-predicted range, and higher than the 2%–8% prevalence in the general pediatric population.²² Biological explanations for increased cryptorchidism risk include: deficiency for Xp22.31 gene product(s), prepubertal hormonal perturbations downstream of *STS* deficiency (e.g., elevated steroid sulfate or luteinizing hormone levels), or disruption of local chromosomal architecture by the genetic deletion and mis-expression of contiguous genes.^{18,23} Despite this apparent vulnerability to structural gonadal abnormalities, the majority of individuals with XLI have preserved fertility and normal sexual development⁸; serum testosterone levels in boys with XLI are equivalent to those in non-affected boys developmentally, but tend to be lower post-pubertally.²³

2.2 | Corneal opacities

In the early-mid 1980s, it was recognized that many males with XLI (and female carriers) presented with corneal dystrophy observable as a 'frosted layer', or small punctate/filiform inclusions usually located deep in the posterior corneal stroma adjacent to, or within, the Descemet basement membrane.^{8,24–26} These proteinaceous bodies may arise as consequence of locally-elevated cholesterol sulfate levels.²⁷ The opacities tend to manifest in adolescence or early adulthood and do not seem to impede visual acuity, although they have occasionally been linked to corneal erosion.⁸ Estimates suggest that opacities may be more common in

males with XLI (prevalence 10%–15%)⁸ than in the general population of USA (<7.5%).²⁸

2.3 | Conditions co-occurring with XLI in rare cases

Historically, a range of syndromes and medical conditions (notably testicular germ cell cancer²⁹) have been described in very few XLI cases.²¹ The rarity of XLI, and often of the comorbid disorders too, makes identification of any consistent relationships challenging.

3 | NEWLY-IDENTIFIED MEDICAL COMORBIDITIES

3.1 | Neurodevelopmental conditions

3.1.1 | Learning disability

After ichthyosis, cognitive impairments (intellectual disability, global developmental delay and delayed speech/language development) are the most commonly-described phenotype in the DECIPHER XLI-relevant cohort, even amongst carriers of typically-sized deletions.¹⁵ However, XLI has not generally been associated with large effects on cognition, and we have shown using the large UK Biobank (UKBB) resource that, whilst middle-aged males carrying typical XLI-associated genetic deletions performed marginally worse than non-carrier males on a fluid intelligence task, the former group performed equivalently to the latter on most other cognitive tasks, and with respect to academic achievement.⁹ However, it should be noted that UKBB is depleted for individuals with neurodevelopmental and/or psychiatric conditions,³⁰ and ~30% of eligible individuals carrying typical XLI-associated deletions may not have been recruited into UKBB (perhaps, in part due to psychological issues).⁹ Hence, the cognitive effects of XLI-associated deletions may be somewhat larger than our UKBB analysis suggests. There have been case reports in the literature of individuals with XLI and learning disabilities; in these cases, the genetic deletions tend to be larger, and often encompass the *VCX3A* (formerly *VCXA*) and/or *NLGN4X* genes.^{20,31–34} Lack of *VCX3A* and/or *NLGN4X* proteins may confer vulnerability to neurodevelopmental conditions,^{35–38} but their deficiency does not inevitably result in gross effects on cognition.^{39,40} Overall, these data suggest that typical XLI-associated deletions alone predispose to mild general cognitive impairment at most, and that the moderate-severe learning disabilities seen infrequently in individuals with XLI (such as those referred to genetics clinics and potentially excluded from UKBB) may be explained by a combination of additional factors: variably-penetrant

deletion of adjacent Xp22.31 genes, the extent/nature of local chromatin disruption, co-segregating genetic variants, environmental exposures and stochastic developmental processes.

The interpretation above is supported by the finding that STS-deficient animal models exhibit normal learning of complex cognitive tasks.^{41–43} Intriguingly, work in such models has shown that deletion of the *STS* orthologue, or inhibition of the STS enzyme, can actually enhance aspects of memory, alter hippocampal neurochemistry, protect against neurodegenerative disease-associated pathology, and increase longevity.^{44–48} Hippocampal volume is comparable in Xp22.31 deletion carriers and non-carriers,⁹ but whether males with XLI exhibit altered hippocampal function, and protection against age-related pathology, is worth investigating in future work.

3.1.2 | Attention deficit hyperactivity disorder

Although attention impairments and hyperactivity were reported in rare *STS*-deficient cases with chromosomal rearrangements in early 2000s,^{49,50} it was not until 2008 that the first case series examining Attention deficit hyperactivity disorder (ADHD) in XLI was described.³³ 40% of boys with XLI assessed met diagnostic criteria for the condition, 80% with the inattentive subtype; the prevalence of ADHD in males from the general population is far lower (≤5%).⁵¹ Later case series across different countries have confirmed that around 30% of boys with XLI meet diagnostic criteria for ADHD, with several co-presenting with other neurodevelopmental conditions including Tourette syndrome, dyspraxia and epilepsy.^{20,21} An online survey comparing self-reported ADHD diagnoses/related traits in males with XLI to those in matched controls confirmed an excess of most traits (apart from ‘motor impulsivity’) in the former group,⁵² a pattern of results recapitulated in female carriers.¹⁹ It is important for individuals affected by XLI and medical professionals to be aware that high levels of neurodevelopmental (or psychiatric) traits in the absence of significant functional impairment can be advantageous and contribute to population neurodiversity.⁵³

Neuroimaging data on individuals with XLI are sparse, and the neurobiological mechanisms mediating increased ADHD likelihood require investigation. Cases with larger (8.4Mb)³² and typically-sized deletions^{54,55} exhibit cortical malformations (heterotopia/dysplasia), but cortical morphology has yet to be systematically investigated. Volumetric analysis of subcortical regions suggests that the smaller size of basal ganglia sub-regions important in maintaining focus and regulating impulse control in deletion carriers may be relevant.⁹ Numerous lines of evidence

implicate *STS* specifically in ADHD-related endophenotypes: (a) individuals with gene-specific point mutations meet diagnostic criteria,³³ (b) the gene is highly-expressed in the developing basal ganglia,⁵⁶ (c) within-gene variation is associated with (in)attentive (but not impulsivity) symptoms in boys with ADHD⁵⁶ and healthy men,⁵⁷ (d) independent mouse models lacking *STS* indicate impairments in attention,^{43,58} reduced motor impulsivity,⁴¹ and altered basal ganglia serotonergic neurochemistry,⁵⁹ and (e) circulating DHEA levels inversely correlate with symptom severity⁶⁰ and are sensitive to pharmacotherapy.⁶¹ The neurobehavioural features and executive function deficits seen in some individuals with XLI could be exacerbated by poor sleep quality (due to night-time discomfort/itching, stress, or aberrant temperature regulation^{62,63}) and, if so, might be ameliorated through sleep-based interventions.

3.1.3 | Autism

Phenotype-first approaches have highlighted a preponderance of *STS*-spanning deletions in people with autism.⁶⁴ In Kent and colleagues' genotype-first approach,³³ boys with XLI were also screened for autism. 20% of participants met diagnostic criteria for this condition or a related language/communication difficulty, a figure markedly higher than the <5% male general population prevalence.⁶⁵ Affected boys possessed larger genetic deletions including the *VCX3A* and *NLGN4X* genes and so deficiency for one (or both) of these genes was suggested as being causal for their behavioural phenotype; however, again, it is possible that other genetic/environmental factors co-segregating with the Xp22.31 deletion are responsible. XLI cases with the typical deletion can present with autism,⁶⁶ and self-reported autism-related traits in males with XLI⁵² and female carriers¹⁹ generally appear to be higher than in matched general population control subjects, implying that loss of gene(s) within the typical deletion interval predisposes to autism-related traits. In both males with XLI⁵² and female carriers¹⁹ the only autism-related trait which is not elevated compared to matched controls is 'attention to detail'. Differing basal ganglia morphology/neurochemistry could partially explain the higher frequency of autism-related traits in individuals with XLI.⁹ *STS*-deficient mice exhibit autism-like features (e.g., perseverative behaviour) highlighting *STS* as a credible gene influencing autism-related traits.⁴²

3.1.4 | Epilepsy

10–15% of individuals with typical XLI deletions have been reported to develop a treatable childhood-onset

form of epilepsy; this often presents as focal epilepsy with centrotemporal spikes.^{21,54,67} The prevalence of epilepsy in boys from the general population is <1%.⁶⁸ In deletion carriers, epilepsy is frequently comorbid with other neurodevelopmental conditions (notably ADHD) suggesting a common cause. Individuals with comorbid XLI and epilepsy have presented with cortical dysplasia⁵⁴ or periventricular leukomalacia,⁶⁷ although others display no clear neuroanatomical abnormalities.⁵⁴ *STS* deficiency appears the prime candidate mechanism for epilepsy predisposition given the *STS* axis' role in modulation of relevant neurotransmitter receptors,⁶⁹ and that a potentially-pathogenic *STS* point mutation has been observed in two brothers with epilepsy.⁷⁰ However, epilepsy-related symptoms have not been observed in *STS*-deficient rodents, so deficiency for alternative Xp22.31 products⁵⁴ or co-segregating factors may confer risk.

3.1.5 | Schizophrenia/psychosis

Genetic risk variants can act pleiotropically to influence both early-onset neurodevelopmental conditions and later-onset psychiatric conditions including schizophrenia.^{71,72} Xp22.31 deletion may elevate schizophrenia risk, particularly against a background of other neurodevelopmental conditions: a young boy with a typical deletion presented with psychotic symptoms consistent with early-onset schizophrenia,⁶⁷ and two females presented with paranoid schizophrenia.⁷³ Additionally, female carriers endorse more schizotypal personality traits than matched non-carriers,¹⁹ and DHEAS levels positively correlate with lifetime psychotic symptom probability in a patient cohort.⁷⁴ Again, *STS* deficiency appears a plausible mechanism.⁷⁵

3.2 | Mood disorders

A convincing association between XLI and elevated mood disorder diagnoses/traits (depression, anxiety and irritability) of comparable magnitude to that seen for psoriasis has recently been demonstrated.^{9,52,76,77} Lower basal ganglia volume, disrupted serotonergic function, and/or altered steroid hormone levels represent candidate biological risk mechanisms.⁹ Putative 'environmental risk' mechanisms include: patient concerns about their appearance and bullying/stigmatisation, the need to manage treatments, side-effects of retinoid-derived medications, medical complications associated with the condition, sleep disturbance, or educational/social challenges linked to neurodevelopmental issues.⁷⁷ Men with XLI perceive the first two of these as being the most strongly-linked to adverse mood symptoms; interventions to improve

TABLE 1 Lines of evidence supporting the role of altered laminin and basement membrane function in X-linked ichthyosis (XLI) extracutaneous phenotypes

Extracutaneous phenotype	Evidence implicating laminin and/or basement membrane pathology
Cryptorchidism	<i>Lamc1</i> (and <i>Ccn1/Cyr61</i>) identified as hub genes by gene expression analysis in a rat model ⁸⁹
Testicular germ cell cancer	Zebrafish mutant for <i>Lamc1</i> susceptible to spontaneous and carcinogen-induced testicular germ cell tumours ⁹⁰
Corneal opacity	Descemet and epithelial basement membranes in the cornea affected in XLI. ^{8,25,91} <i>LAMC1</i> genetically-associated with Fuch's endothelial corneal dystrophy, a condition linked to thickening of the Descemet membrane due to excessive extracellular matrix deposition ⁹²
Neurodevelopmental conditions	LAMC1 mediates cortical histogenesis and its abnormal expression results in disrupted basement membrane structure and cortical dysplasia. ⁹³ Laminin protein disruption associated with cortical heterotopias in man ⁹⁴ . <i>LAMC1</i> shows genetic association with cortical folding and thickness, ^{95,96} the latter robustly differentiating ADHD, autism and schizophrenia cases from controls ^{97,98}
Cardiac arrhythmia	General basement membrane dysfunction implicated in cardiovascular pathologies including arrhythmia. ⁹⁹ Laminin (including LAMC1) protein levels differ in patients with and without atrial fibrillation. ^{100,101} <i>LAMC1</i> gene implicated in arrhythmia. ¹⁰² Laminins (including LAMC1) important in regulation of heart looping, atrial growth and cardiac size during development. ¹⁰³ <i>LAMC1</i> -mutant cardiomyocyte cultures display impaired electrical signal propagation ¹⁰⁴
Dupuytren's contracture	Disrupted basal lamina structure, and high laminin (including LAMC1) and CTGF (CCN2) expression, in palmar fascial nodules ^{105–107}
Hemorrhage	Hemorrhage risk increased in <i>Lamc1</i> mutant mice due to impaired function of the basement membrane ensheathing the vasculature ^{93,108}

societal knowledge of ichthyosis and thereby destigmatise it, together with advice related to treatment sourcing/application, and a holistic approach to multi-disciplinary care, would likely mitigate mood issues.⁷⁷

3.3 | Cardiac arrhythmias

Middle-aged males carrying typical XLI-associated deletions are around four times more likely to have been diagnosed with atrial fibrillation/flutter (AF) than their non-carrier counterparts (10.5% vs. 2.7% of UKBB participants respectively),⁹ and AF affected one middle-aged male with XLI described in a recent case report.⁷⁸ AF is a type of irregular heart rhythm which increases heart failure, stroke, and dementia risk, and, as such requires early identification, monitoring and treatment.⁷⁹ The higher burden of cardiac arrhythmias in deletion carriers could, theoretically, be due to side-effects of medication use specific to this group for example, retinoid-based medications for ichthyosis or stimulant medications for ADHD.⁸⁰ Use of these medications in UKBB sample was very low and did not differ by group,⁹ and there is little evidence that ichthyosis treatments promote arrhythmia, so a biological predisposition to cardiovascular risk appears more likely. Structural heart abnormalities, but not arrhythmias, have been reported in 7% of the predominantly-young

DECIPHER XLI-relevant cohort (ventricular-septal defect and abnormal valve morphology),¹⁵ and an abnormal heart rhythm has only been reported in one boy with XLI.⁸¹ Cardiac arrhythmias might manifest in adulthood in deletion carriers with underlying structural heart issues.

Our ongoing (unpublished) work in UKBB indicates that males with XLI and abnormal heart rhythms are disproportionately likely to be affected by gastrointestinal issues, and that *STS* is the only protein-coding Xp22.31 gene harbouring an excess of common risk variants for idiopathic AF. The finding that cancer patients pre-screened for existing heart rhythm anomalies occasionally present with these following *STS* inhibition⁸² further supports *STS* deficiency as a mechanism for arrhythmia risk. *STS* deficiency could feasibly mediate risk via effects on cardiovascular circulation, DHEA(S) levels, cholinergic signalling and/or fibrosis.⁷⁹

3.4 | Dupuytren's contracture

Dupuytren's contracture, in which one or more fingers become permanently flexed, typically onsets in middle-age due to fibrosis of the palmar fascia.⁸³ In UKBB, we identified diagnosis in 3.5% of male deletion carriers (compared to 0.6% in non-carriers),⁸⁴ and the DECIPHER

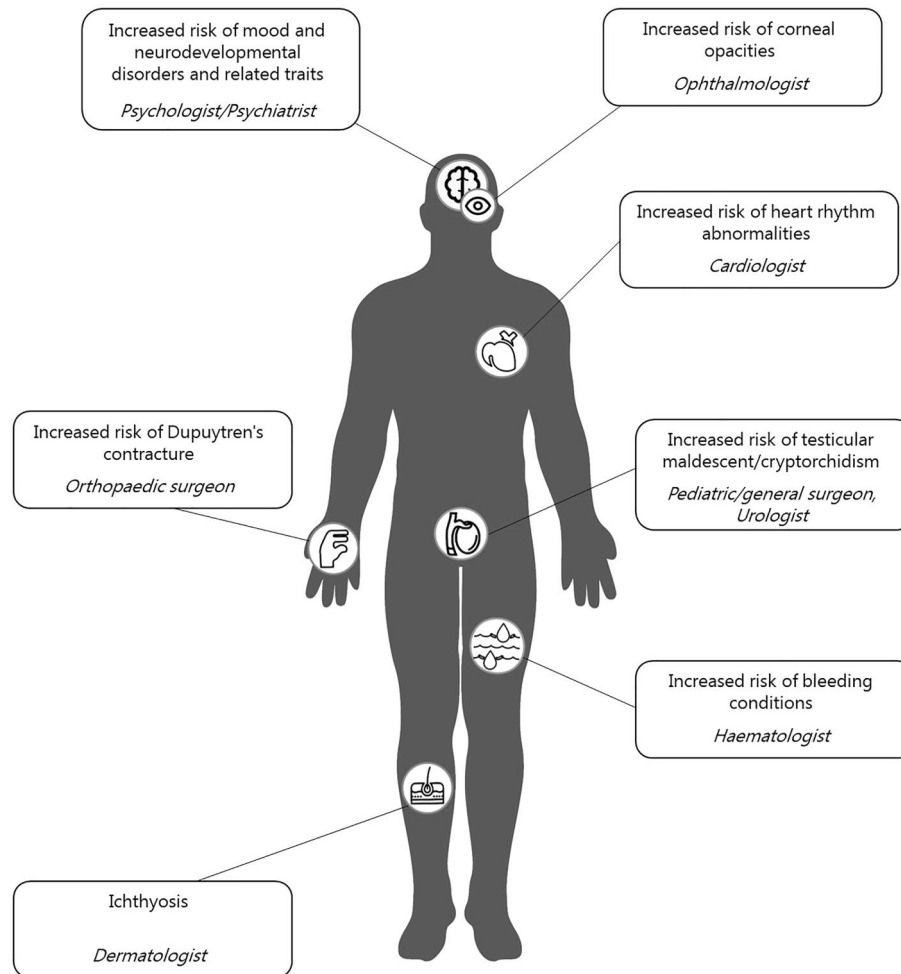


FIGURE 1 A summary of cutaneous and extracutaneous symptoms associated with X-linked ichthyosis (XLI), and clinicians relevant for multidisciplinary care of affected individuals.

database describes one patient with a pathogenic point mutation within *STS* and contracture of the 5th finger.¹⁵

3.5 | Bleeding conditions

Work in UKBB also identified a specific bleeding-related phenotype ('hemorrhage or hematoma complicating a procedure') as being more common (3.5%) in deletion-carrying males than male non-carriers (0.5%).⁸⁴ This finding could reflect the fact that deletion carriers undergo more, or more invasive, procedures than non-carriers and/or that deletion carriers are more likely to be prescribed retinoid-derived pharmacotherapy with adverse effects on blood-clotting.⁸⁵ Alternatively, and perhaps more likely given that no deletion carriers reported being prescribed such medications, it could have a biological explanation. Relevantly, *STS* is most highly-expressed in the adult arterial vasculature¹⁷ and cholesterol sulfate is a known endogenous haemostatic modulator.⁸⁶

4 | A LINK BETWEEN COMORBIDITIES?

The conditions linked to XLI above appear disparate in their presentation, and in the bodily systems they affect. Is it the case that a common pathophysiological process, induced by deficiency for one or more Xp22.31 gene(s), is responsible, and, if so, could this be targeted pharmacologically?

Few data currently exist on the molecular pathways disrupted *in vivo* by XLI. One study comparing skin gene expression in affected and unaffected individuals identified just 6 genes outside the Xp22.31 region the expression of which differed by > 3-fold: *GDA*, *UPK1A*, *LAMC1*, *PPME1*, *KLK9* and *MLL5*.⁸⁷ *LAMC1* encodes the gamma 1 subunit of the heterotrimeric laminin complex, a critical constituent of the extracellular matrix (ECM) basement membrane to which the interstitial ECM adheres.⁸⁸

On the basis of multiple lines of evidence (Table 1), we propose that extracutaneous phenotypes associated with XLI may be partially explained by perturbed

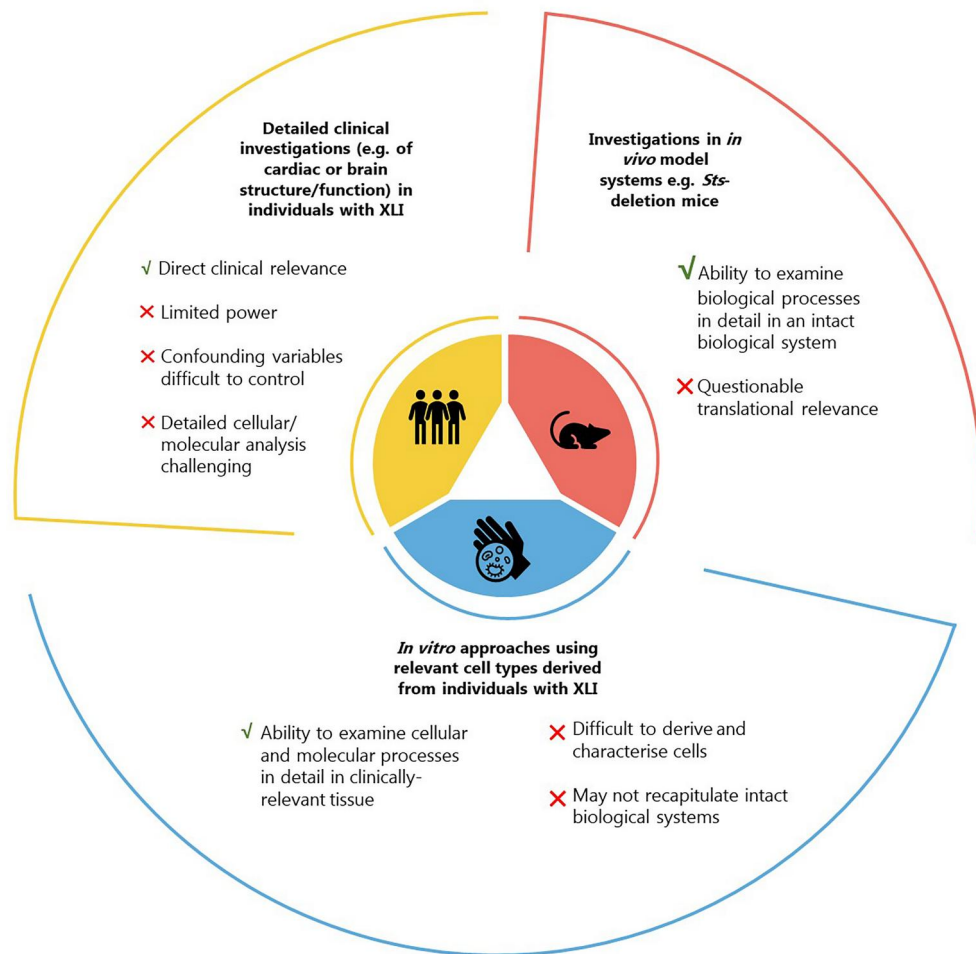


FIGURE 2 Potential approaches to understand the pathophysiology of extracutaneous phenotypes associated with X-linked ichthyosis (XLI).

ECM function, and specifically fundamental changes to laminin expression and basement membrane integrity. Subsequent disruption to cross-talk between basement membrane and matricellular proteins (such as the Cellular Communication Network factors (CCNs) known to be sensitive to STS deficiency¹⁰⁹) might predispose to (extra)cellular pathophysiology including fibrosis.

5 | CONCLUSIONS

Individuals with XLI are at greater likelihood of being affected by various medical conditions, which can impact their education, quality of life, morbidity and mortality (Figure 1). Future high-powered studies in geographically/ethnically-diverse populations should aim to replicate, extend, and further characterise, the associations discussed above. Specifying the prevalence, nature and co-occurrence of comorbidities and disseminating findings to individuals affected by XLI and their family members, treating clinicians, and genetic counsellors

should facilitate early detection of problems and referral to appropriate medical specialists (Figure 1), with ensuing benefits in terms of treatment efficacy.

Understanding the physiological, cellular and molecular processes underlying XLI comorbidities will require work across experimental paradigms (Figure 2). Detailed phenotyping in individuals with XLI might include psychiatric/neuropsychological evaluations, imaging and monitoring of electrical signals of the brain and heart, and multi-omic analysis of accessible tissues; however, recruiting sufficient participants to ensure adequate power and to address confounds may be challenging. *In vitro* cellular or organoid models with engineered STS mutations, exposed to STS-knockdown, or derived from patient tissues, might be useful to examine condition-related cell biology processes, but their generation can be challenging and findings may not reflect whole organism physiology. Arguably, investigations in preclinical models in which the *Sts* gene is specifically targeted may be the most appropriate way to address multisystemic conditions, although given species differences in steroid hormone biochemistry, and

organ structure/function, their translational relevance is questionable. Should (pre)clinical or cellular studies uncover support for abnormal ECM function in XLI, laminin and CCN proteins could represent viable pharmacotherapeutic targets. ^{110–112}

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Georgina H. Wren: Visualization (lead); Writing – original draft (supporting); Writing – review & editing (equal). **William Davies:** Conceptualization (lead); Funding acquisition (lead); Supervision (lead); Writing – original draft (lead); Writing – review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

ETHICS STATEMENT

Not applicable.

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