The importance of cardiac screening in X-linked ichthyosis – a plea

William Davies[1,2,3]*

[1]Division of Psychological Medicine and Clinical Neurosciences and Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff, UK

[2]School of Psychology, Cardiff University, Cardiff, UK

[3]Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK

*to whom correspondence should be addressed:

Dr William Davies, 70, Tower Building, Park Place, Cardiff CF10 3AT, UK

Tel:+44-(0)29-2087-0152

e-mail: daviesw4@cardiff.ac.uk

Conflict of interest statement: The author has no conflicts of interest to declare.

Dear Editor,

X-linked ichthyosis (XLI) is a rare dermatological condition almost exclusively affecting males, which is characterised by abnormal desquamation and a retention hyperkeratosis [1]. The condition results from loss-of-function of the enzyme steroid sulfatase, most commonly as a consequence of Xp22.31 microdeletions encompassing the *STS* gene [1]. In addition to dermatological issues, individuals with XLI can present with a range of extracutaneous symptoms [1]. Female carriers of XLI-associated genetic variants do not typically present with ichthyosis or associated extracutaneous features, but can display elevated levels of related traits relative to female non-carriers.

Using the UK Biobank, a large population cohort of almost half a million participants, my research group discovered an unexpected association between Xp22.31 microdeletions encompassing *STS* and a substantially-increased risk (approximately fourfold) of developing atrial fibrillation/flutter (AF) in middle-aged males [1]; subsequent genetic association analysis in the same large cohort indicated *STS* as the most likely causal candidate gene within the deletion interval [2]. AF is a cardiac arrhythmia (abnormal heart rhythm) characterised by rapid and/or irregular beating of the heart's atria. Work extending these initial findings, and employing an online survey approach in boys and men with XLI, and in adult female carriers, confirmed a high prevalence (28-35%) of self-reported heart rhythm abnormalities across each of these three groups [2]; reported abnormalities included AF and brady- and tachycardia (excessively slow or rapid heart rate respectively). This follow-up study indicated stress, exercise, and increased body temperature as identifiable precipitants of arrhythmic episodes. Several comorbidities associated with arrhythmia risk in these three groups were also highlighted: the most robust of these associations was with gastrointestinal issues, and weaker associations were seen with asthma, anaemia and 'heart valve disease or malformation'. The physiological basis of increased arrhythmia risk in XLI has yet to be systematically investigated, but limited existing data from clinical cases and from a laboratory study examining gene pathways sensitive to *STS* downregulation, have implicated septal defects as a contributory factor [3].

Abnormal heart rhythms can, over time, result in heart failure i.e. an inability of the organ to deliver sufficient blood around the body. Moreover, such rhythms can result in slowed or turbulent cardiovascular blood flow, leading to an increased likelihood of thrombosis and subsequent embolism. Cerebral embolism can cause stroke, and contribute to cognitive decline and dementia risk. Heart failure, stroke and cognitive decline are long-term health conditions impacting significantly on affected individuals and their loved ones, requiring extensive medical and social care, and placing a considerable burden on healthcare systems.

A recently-published case report graphically illustrates that XLI, in addition to predisposing to multiple chronic conditions, may also be associated with acute, life-threatening, cardiac complications in young adults [4]. The report describes a 17 year male who collapsed suddenly and went into cardiac arrest with ventricular fibrillation; subsequent electrocardiography (ECG) revealed a wandering atrial pacemaker, ST-segment elevation, and T-wave inversion with a high frequency of ventricular extrasystoles (VEs), while echocardiography indicated a structurally and functionally normal heart. Whole exome sequencing detected a genomic deletion including *STS* in the affected individual, consistent with previously-unrecognised XLI. The patient was eventually discharged after a prolonged hospital stay. Through my ongoing interactions with individuals with XLI and their families on social media, I have become aware of several other cases of individuals with XLI dying, or almost dying, from sudden cardiac arrhythmia, including adolescents and young adults.

The emerging findings outlined above require publicising to relevant stakeholders with a view to identifying relevant symptoms as early as possible in patients, and intervening where necessary for maximum therapeutic benefit and to mitigate long-term adverse effects on health. We are currently

attempting to do this through working with clinicians involved in diagnosing and treating XLI, relevant charities, and social media patient support groups. We recommend that upon being definitively diagnosed with XLI, individuals are routinely asked about cardiac issues and are referred for specialist evaluation by cardiologists if they report ongoing arrhythmia-related symptoms e.g. palpitations, chest pain, breathlessness, extreme anxiety, dizziness or fainting, and fatigue; individuals with XLI and the comorbidities referenced above might also be prioritised for onward referral. Where possible, patients' relatives who might feasibly carry an XLI-associated genetic variant should also be genetically-tested and assessed for cardiac issues (so-called 'cascade screening'). Our previous work has shown that individuals with XLI and female carriers are amenable to the idea of cardiac screening [2]. In future, ongoing heart rhythm monitoring may be undertaken in 'at risk' individuals through the use of wearable technologies; importantly, such monitoring can identify asymptomatic arrhythmias. Recent pilot data has suggested that smartwatches may be useful in this regard, and has reinforced the notion of a link between XLI and specific aspects of cardiac function (bradycardia and a high burden of VEs) in some individuals [5]. Larger studies to determine the utility of this screening approach need to be undertaken.

1. Brcic L, Underwood JFG, Kendall KM *et al*. Medical and neurobehavioural phenotypes in carriers of X-linked ichthyosis-associated genetic deletions in the UK Biobank. *J Med Genet* 2020; **57**: 692-698.

2. Wren G, Baker E, Underwood J *et al*. Characterising heart rhythm abnormalities associated with Xp22.31 deletions. *J Med Genet* 2023; **60**:636-643.

3. Wren GH, Davies W. Cardiac arrhythmia in individuals with steroid sulfatase deficiency (X-linked ichthyosis): candidate anatomical and biochemical pathways. *Essays Biochem* 2024; **68**:423-429.

4. Mutlu H, Kayihan C, Ay A *et al*. Sudden cardiac arrest in an adolescent with X-linked ichthyosis. *Anatol J Cardiol* 2025; **XX**:1-3. doi: 10.14744/AnatolJCardiol.2025.4903

5. Wren GH, O'Callaghan P, Zaidi A *et al*. Monitoring heart rhythms in adult males with X-linked ichthyosis using wearable technology: a feasibility study *Arch Dermatol Res* 2025; **317**:351.