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X-linked Ichthyosis: New Perspectives on a Disease that Affects Multiple Systems

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Description

The dry, thickened scales of the ichthyoses are dermatological conditions caused by abnormal cornification and desquamation processes. An ichthyosis subtype that is inherited as an X-linked recessive trait (that is, it is passed from unaffected female carriers to sons) was discovered in the early 20th century. The STS gene was subsequently cloned after biochemical studies in affected individuals' skin fibroblasts correctly predicted a lack of the enzyme Steroid Sulfatase (STS) as a cause. Multiple steroid hormones, including Dehydroepiandrosterone Sulfate (DHEAS), are cleaved by STS, affecting their water-solubility, bioavailability, and activity. In "X-Linked recessive Ichthyosis" (XLI), the skin phenotype is probably caused by an excess of cholesterol in the stratum corneum and an accumulation of cholesterol sulfate. The majority of affected males inherit an Xp22.31 genetic deletion from a heterozygous carrier mother, and clinically, XLI presents with widely dispersed polygonal, translucent scales that gradually give way to large, darker brown-grey scales primarily on the neck, trunk, and extensor surfaces. This includes STS and its immediate neighbors (the protein-coding genes PUDP(HDHD1), VCX, and PNPLA4, as well as the non-coding microRNA MIR4767), and it can be STS-specific. It typically has a size of 1.5–1.7 Mb. The remaining XLI cases have a STS point mutation or, in rare instances, a larger deletion that affects a number of adjacent genes. "Syndromal ichthyosis" refers to the condition in which a person has multiple developmental issues in addition to their extensive deletions. The majority of our focus here is on typical "non-syndromic" XLI cases.

Clinical Genetics

One in 1500 men in the general population are thought to have typical Xp22.31 deletions, but as few as one in 6,000 men are diagnosed with XLI, according to prenatal screening studies. This suggests that STS deficiency is linked to a wide range of skin conditions, and that many carriers either does not receive an XLI diagnosis or are misdiagnosed. As a result, people who were identified genetically had skin phenotypes that were less severe than those found in dermatology clinics. In addition, ichthyosis or a "skin abnormality" is identified in approximately 60% of phenotypically-characterised males with Xp22.31 deletions 10 Mb around STS reported in the DECIPHER clinical genetics database (the "DECIPHER XLI-relevant cohort"). An individual's background genetics, particularly variants in the autosomal FLG (filaggrin) gene, may alter the severity of XLI.

Deficits in the Xp22.31 gene products may be associated with extracutaneous medical phenotypes due to their widespread expression in the human body. The rarity of XLI, the unnecessary phenotyping of cases, and ascertainment biases have hampered the recognition of such phenotypes (cases have primarily been identified in dermatology clinics based on their moderate-severe skin condition, and they are frequently young). New genotype-phenotype associations have emerged as a result of improved recruitment across the age range, genotyping/phenotyping, and data collection and dissemination strategies (particularly through large-scale biobanks and clinical genetics resources).

Hormonal Disturbances

A possible connection between XLI and bilateral or unilateral cryptorchidism (testicular maldescent into the scrotum during development) 18 was highlighted in case reports and series published in the late 1970s and early 1980s. In these early studies, cryptorchidism was found in 10%–40% of people with XLI, especially in those whose births were hampered by obstetric problems (placental STS deficiency delays or prolongs labor in >60% of carrier mothers19). Cryptorchidism prevalence rates in more recent case series and the DECIPHER XLI-relevant cohort are consistent with the lower end of the initially predicted range and higher than the 2%–8% prevalence in the general pediatric population. The following are biological explanations for an increased risk of cryptorchidism: a lack of the Xp22.31 gene product(s), prepubertal hormonal disturbances that occur after STS deficiency (such as elevated levels of steroid sulfate or luteinizing hormone), or a genetic deletion and mis-expression of contiguous genes that disrupt local chromosomal architecture. The majority of people with XLI have maintained fertility and normal sexual development, despite this apparent susceptibility to structural gonadal abnormalities; Boys with XLI have serum testosterone levels that are comparable to those of boys without the condition during development, but they tend to be lower after puberty. During the early to mid-1980s, it became clear that a lot of male XLI patients and female carriers had corneal dystrophy that could be seen as a "frosted layer," which was small punctate or filiform inclusions that were usually deep in the posterior corneal stroma, either next to or within

the descemet basement membrane. These proteinaceous bodies may develop as a result of elevated cholesterol sulfate levels in a particular location. Although they have occasionally been linked to corneal erosion, the opacities do not appear to affect visual acuity and typically appear in adolescence or early adulthood. Opacities may be more common in males with XLI (prevalence 10%–15%) than in the general population of the United States (7.5%), according to estimates. In the DECIPHER XLI-relevant cohort, cognitive impairments (intellectual disability, global developmental delay, and delayed speech/language development) are the most frequently described phenotype following ichthyosis, even among carriers of deletions of typical size. While middle-aged males with 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 in terms of academic achievement. However, XLI has not typically been associated with significant effects on cognition. We have demonstrated this using the extensive UK Biobank (UKBB) resource. However, it should be noted that UKBB is depleted for people with neurodevelopmental and/or psychiatric conditions. Additionally, less than 30% of eligible people with typical XLI-associated deletions may not have been recruited into UKBB (perhaps in part due to psychological issues). As a result, our UKBB analysis suggests that the cognitive effects of XLI-associated deletions may be somewhat larger. The literature contains case reports of people with XLI and learning disabilities; The VCX3A (formerly VCXA) and/or NLGN4X genes are frequently included in these larger genetic deletions. Although a deficiency in either the VCX3A or NLGN4X proteins can make a person more susceptible to neurodevelopmental conditions, it is not always the case that this will have a significant impact on cognition. Overall, these data suggest that typical XLI-associated deletions only predispose to mild general cognitive impairment, and that the moderate-severe learning disabilities that are rarely seen in people with XLI (like those who are referred to genetics clinics and may be excluded from UKBB) may be explained by a combination of additional factors: the extent and nature of local chromatin disruption, co-segregating genetic variants, environmental exposures, and stochastic developmental processes, as well as variably-penetrant deletion of adjacent Xp22.31 genes.

The fact that STS-deficient animal models exhibit normal learning of complex cognitive tasks lends credence to the preceding interpretation. Intriguingly, studies in these models have demonstrated that inhibiting the STS enzyme or deleting the STS orthologue can actually improve aspects of memory, alter hippocampal neurochemistry, protect against pathology that is associated with neurodegenerative diseases, and prolong life. Although carriers and non-carriers of the Xp22.31 deletion have comparable hippocampal volumes, future research should focus on determining whether males with XLI have altered hippocampal function and are protected against age-related pathology.