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STS pathogenic variants in a Dutch patient cohort clinically suspected for X-linked ichthyosis show genetic heterogeneity

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Dear Editor, X-linked ichthyosis (XLI) is the second most common ichthyosis after ichthyosis vulgaris (IV).[1] Despite their differences, it can be challenging to clinically distinguish the different patient groups. Whereas IV is mainly caused by loss-of-function variations in the filaggrin gene (*FLG*),[2,3] XLI is predominantly (85–90%) caused by deletion of the entire steroid sulfatase gene (*STS*).[1,4] Nevertheless, other pathogenic variants are found, currently encompassing 81 unique pathogenic variants in the Leiden Open Variation Database (LOVD v.3.0).

In this large Dutch cohort, 109 male patients clinically suspected of having XLI were included for genetic diagnosis at the Maastricht UMC+ by the patient's dermatologist or clinical geneticist affiliated with various Dutch hospitals. Only limited clinical information on the patients' phenotypes was available. The institutional review board of the Maastricht UMC+ approved the study. All DNA samples were first analysed by multiplex ligation-dependent probe amplification (MLPA) (kit P160-C1; MRC Holland, Amsterdam, the Netherlands) for copy number variant detection to identify entire gene deletions of *STS*, often found in XLI. If MLPA was normal, subsequent Sanger sequencing of the *STS* coding exons and splice sites was performed. Enzymatic STS activity was tested in patients' leucocytes (Amsterdam UMC, Laboratory Genetic Metabolic Diseases) to further classify variants, when predictive computational analyses was not conclusive (Alamut Visual v.2.15; SOPHiA GENETICS, Saint Sulpice, Switzerland). Sequential targeted single-molecule molecular inversion probe analysis for *FLG*[3] and/or whole-exome sequencing[5] was requested in some patients only when considered necessary by the patient's physician.

In 71 patients (65%) an *STS* pathogenic variant was detected (Figure 1a). The majority of patients with XLI (57, 80%), showed the frequently found genomic deletion of the entire *STS* gene and flanking *PUDP* sequence containing at least chrX.hg19: g.(?_6968202)_(7269849_?)del. This finding more accurately portrays the frequency in comparison with previous, smaller cohort studies.[1,4] Detection of copy number variants further uncovered a deletion of the complete *STS* gene without the *PUDP* sequence, an exon 6 deletion and a duplication of exons 8–9 in three individual patients. Subsequent Sanger sequencing identified one patient with a splice-site variant, six patients with missense variants, one patient with a nonsense variant, and three patients with a frameshift variant (Figure 1b). The variants were classified according to the American College of Medical Genetics guidelines.[6] The variant c.1253A>G p.(Asp418Gly) was classified as likely to be benign due to normal STS enzymatic activity in the patient's blood. As a result, 11 novel *STS* (probable) pathogenic variants were identified, of which four resulted in no enzymatic activity (Figure 1b). The remaining novel missense variants were primarily classified based on variants published as pathogenic at equivalent positions in paralogue sulfatase genes (*GALNS*, *ARSL*). In total, the number of known mutations in LOVD was increased by 14%.

Additional analysis of *FLG* was performed in 66 patients (61%). In 23 patients (21% of the total cohort) loss-of-function variants in *FLG* were detected, which had a similar variant distribution to the Dutch population (72% frequent, 28% rare),[3] as well as one novel *FLG* variant, NM_002016.2:c.4297G>T p.(Glu1433*). Of these, 19 patients (17%, six of 19 heterozygotes) were incorrectly clinically diagnosed with XLI while actually having IV. This emphasizes the challenges that physicians encounter in clinically distinguishing the different forms of ichthyosis. In at least four cases (4%) the *FLG* variant was concomitant with an *STS* pathogenic variant (Figure 1a), potentially exacerbating XLI in these patients.[2] The modifying effect could not be evaluated in these patients, as an intrafamilial reference patient only having the *STS* variant was not available.

Furthermore, whole-exome sequencing in three patients identified previously published pathogenic variants in *SDR9C7*: NM_148897.3:c.[551A>G];[703G>A] p.[(Asp184Gly)];[(Gly235Arg)], *ALOXE3*: NM_021628.3:c.[1889C>T];[1889C>T] p.[(Pro630Leu)];[(Pro630Leu)], and *NIPAL4*: NM_001099287.1:c.[527C>A];[527C>A] p.[(Ala176Asp)];[(Ala176Asp)], associated with types of autosomal recessive congenital ichthyosis (ARCI).

For 43 patients (39% of the total) sequential analysis was not requested. In 16 patients (15%) no pathogenic variants were identified with the tests performed. Therefore, it is conceivable that some patients only tested for *STS* and without variants (four of 16 patients, 25%) could actually have variants associated with IV or ARCI. Moreover, the proportion of patients carrying concomitant pathogenic variants of *STS* and *FLG* may be underestimated as only 30 of 71 patients with confirmed XLI (42%) were tested for both genes (Figure 1a).

Confirmation of diagnoses through genetic analyses is important as the clinical consequences are different for patients with XLI and IV. Patients with XLI need genetic counselling as their mothers and future daughters, being obligate carriers, may have a complicated delivery of (another) affected son,[7] while patients with IV are prone to develop atopic dermatitis, allergies and asthma.[8] Considering our results and all these factors influencing the diagnostic process in XLI, we recommend analysis for both *STS* and *FLG* in male patients clinically suspected for XLI, and extended analysis should be considered for other ichthyosis subtypes (ARCIs) when genetic diagnosis remains elusive.

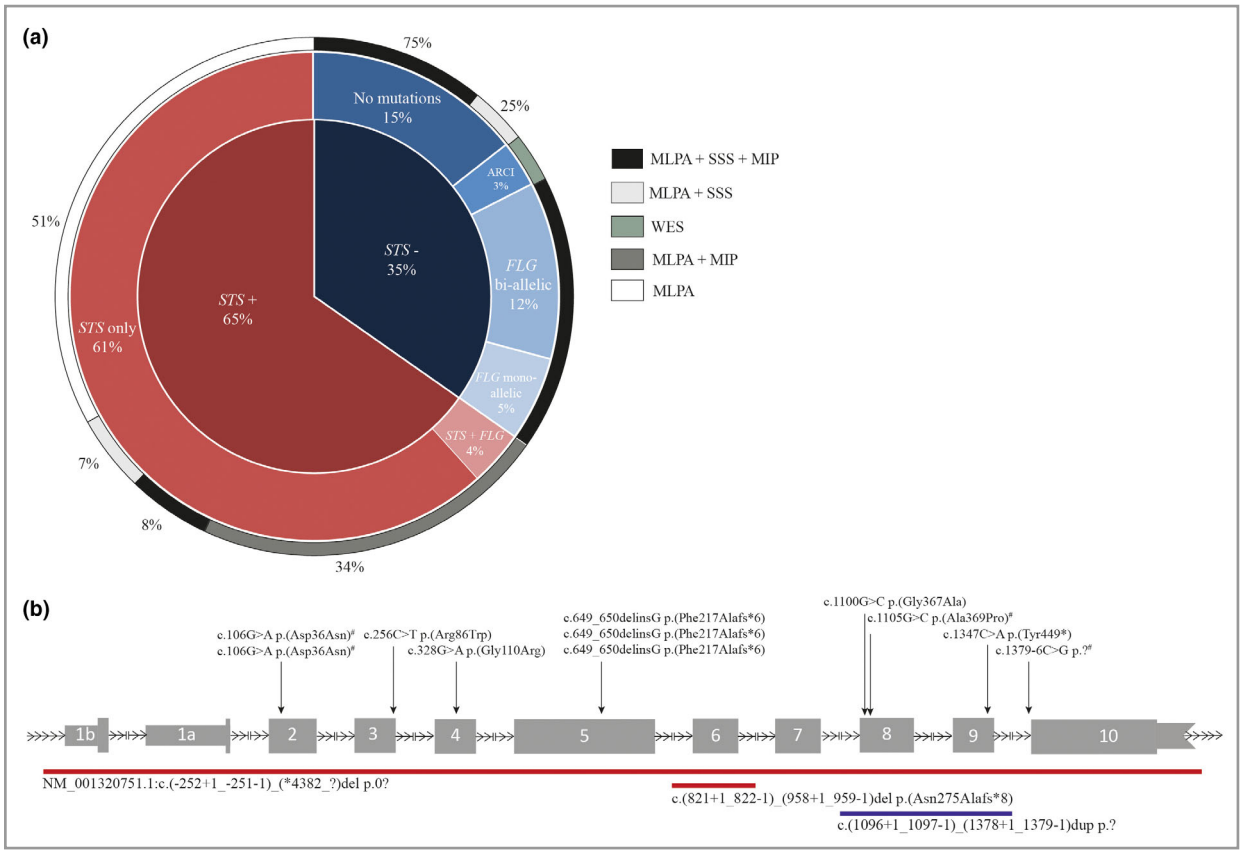

Figure 1 (a) Distribution of pathogenic variants in the Dutch cohort. The inner circle represents the proportion of patients with variants in *STS*. The middle circle shows patients with only *STS* variants, concomitant variants, *FLG* variants, autosomal recessive congenital ichthyosis (ARCI)-associated variants, or no pathogenic variants. The outermost circle represents the genetic analysis performed within subgroups of the cohort. MIP: *FLG* single-molecule molecular inversion probe analysis, MLPA: multiplex ligation-dependent probe amplification, SSS: Sanger sequencing *STS*, WES: whole-exome sequencing. (b) Distribution of novel pathogenic variants in *STS*. Gene structure (scaled) of *STS*: 10 exons (with alternate exons 1a and 1b representing different isoforms) and two deletions (red), one duplication (blue), and nucleotide variants (arrows) for each patient. Data are based on NCBI RefSeq:NM_000351.5. #Steroid sulfatase (STS) enzymatic activity absent. All variants were submitted to the public Leiden Open Variation Database with their corresponding classification.

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Clinical, dermoscopic and histopathological findings in localized human monkeypox: a case from northern Italy

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Dear Editor, The recent monkeypox (MP) outbreak is an increasingly alarming public health concern, as multiple clusters are being identified throughout Europe, especially in men who have sex with men (MSM).[1–3] This emerging zoonotic disease is transmitted through intimate contact and air droplets, with the possibility of spread via sexual fluids still under investigation.[2,4,5]

A 44-year-old Ukrainian individual, identifying himself as an MSM, presented to the sexually transmitted diseases outpatient service of our dermatology unit in Milan for an asymptomatic cutaneous eruption that had appeared 5 days before on his external genitalia and the third finger of his right hand. Prior to the appearance of skin lesions, he had reported low-grade fever, headache and malaise for a week.

His medical history was positive for past nodal tuberculosis and untreated chronic hepatitis C virus infection. Moreover, he was HIV-1 positive and currently under combination antiretroviral therapy (CD4 count $0{\cdot}935 \times 10^9$ cells L^{-1}; HIV viral load < 200 copies mL^{-1}). Recently, he had also been treated for primary syphilis, with normalization of serum rapid plasma reagin titre. It is noteworthy that he had not been vaccinated for smallpox. The patient did not recall being in close contact with animals and denied travelling abroad in the past year, but mentioned numerous occasions of condomless sexual intercourse in the preceding months.

Upon physical examination, multiple vesiculopustular lesions approximately in the same stage of development were noted on the patient's scrotum, penis, right thigh and distal phalanx of the third finger of his dominant hand, some with marked umbilication and central crusting (Figure 1a, b). Tender, bilateral inguinal lymphadenopathy was found on palpation. Dermoscopy showed whitish structureless areas with brownish central crusts and perilesional erythema (Figure 1a; inset).

On histology, a central area of full-thickness epidermal necrosis with adjacent acanthosis and keratinocyte degeneration was shown – possibly corresponding to the whitish halo observed on dermoscopy – along with exocytosis of lymphocytes, neutrophils and rare eosinophils (Figure 1c). Keratinocytes displayed cytopathic changes consisting of an eosinophilic 'ground glass' appearance of the nucleus. The underlying dermis revealed a full-thickness inflammatory

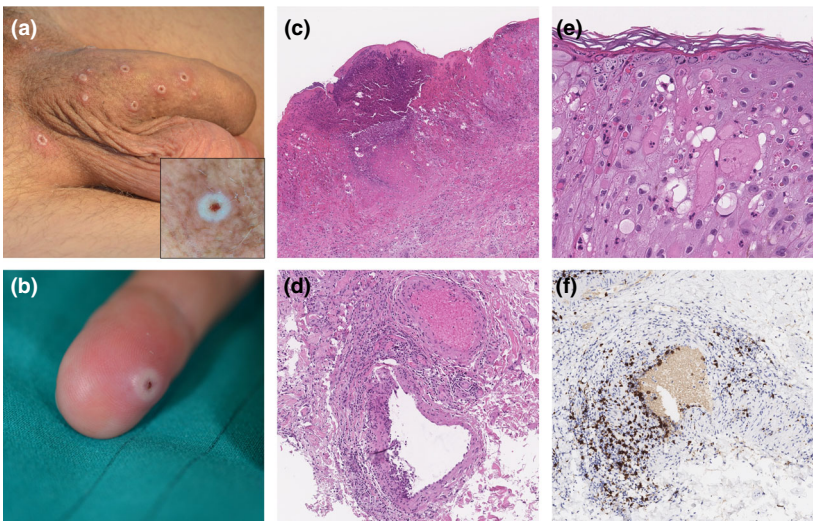

Figure 1 (a) Typical vesiculopustular lesions, predominantly distributed on the patient's genitalia. Dermoscopy revealed whitish structureless areas with brownish central crusts and perilesional erythema (inset). (b) A single pustular element on the third finger of the patient's dominant hand was observed. (c) On histology, full-thickness epidermal necrosis with surrounding acanthosis and keratinocyte degeneration was demonstrated [haematoxylin and eosin (H&E), original magnification × 40]. (d) Signs of vessel wall involvement were also noted (H&E, × 200). (e) At higher magnification (H&E, × 400), rare multinucleated keratinocytes were seen, together with eosinophilic, homogeneous spherical intracytoplasmic inclusions (Guarnieri bodies). (f) On immunohistochemistry, angiotropic $CD8^+$ T cells colocalized with cytopathic changes (anti-CD8 monoclonal antibody; Dako, Glostrup, Denmark; clone C8/144B, peroxidase, × 200).