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Pre-Descemet Corneal Dystrophy and X-linked Ichthyosis Associated with Deletion of Xp22.31 Containing the *STS* Gene

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Abstract

Purpose—To report the association of X-linked ichthyosis and pre-Descemet corneal dystrophy with a deletion of the steroid sulfatase gene (*STS*) detected with microarray-based comparative genomic hybridization (aCGH).

Methods—A slit lamp biomicroscopic and cutaneous examination were performed, after which a saliva sample was collected as a source of genomic DNA. PCR amplification of each of the 10 exons of *STS* was performed, as was aCGH on genomic DNA to detect copy number variation (CNV).

Results—Slit lamp examination revealed punctate opacities in the posterior corneal stroma of each eye. Cutaneous examination demonstrated scaling and flaking skin of the arms and legs. PCR amplification using primers designed to amplify each of the 10 exons of *STS* failed to produce any amplicons. Subsequently, aCGH performed on genomic DNA revealed a microdeletion in the Xp22.31 cytoband of approximately 1.7 megabases, containing *STS*.

Conclusions—The identification of a microdeletion within Xp22.3 containing *STS* with aCGH in an individual with suspected pre-Descemet corneal dystrophy and X-linked ichthyosis demonstrates the clinical utility of CNV analysis in confirming a presumptive clinical diagnosis.

Keywords

ichthyosis; pre-Descemet corneal dystrophy; steroid sulfatase deficiency; *STS*

INTRODUCTION

The term ichthyosis refers to a “fish scale” appearance of the skin in patients afflicted with this condition.¹ While ichthyosis may have a variety of etiologies, the term is most commonly used to describe hereditary disorders of skin keratinization. The ichthyotic dermatoses are classified into 4 categories based on the mode of inheritance and the characteristic clinical manifestations: ichthyosis vulgaris (the most common), X-linked ichthyosis (XLI), lamellar ichthyosis, and bullous ichthyosiform erythrodermia.^{1, 2} XLI, the second most common form of ichthyosis with a reported incidence of 1 in 1500 to 6000 males, usually presents within the first year of life with the appearance of large, hyperpigmented scales primarily on the extensor surfaces of the limbs and on the side of the torso.^{3, 4} While other areas of the body may be affected, the lower extremities usually demonstrate the most significant cutaneous changes after early childhood.⁵

XLI is due to a deficiency of the enzyme steroid sulfatase (*STS*; MIM 300747), which has been mapped to the Xp22.3 locus on the distal short arm of the X-chromosome, a region associated with a high frequency of deletions.⁶ While 80–90% of XLI cases result from complete deletions of *STS*, a few case reports have described point mutations in the gene, and a small number of cases may be due to genetic alterations of the X chromosome that do not affect *STS*.^{5, 7} XLI may occur solely as a skin disorder, or be associated with other findings such as ocular changes (up to 50%), cryptorchidism (20%), chondrodysplasia punctata, mental retardation, and epilepsy.⁵ Several syndromes have been described that involve deletion of *STS* and adjacent genes, such as Rud, Conradi, and Kallmann syndromes.⁵ Ocular findings in ichthyoses are varied, and include changes in the lids, conjunctiva, cornea, lens and peripheral retina.^{8, 9} In particular, the myriad corneal changes associated with XLI may involve all layers of the cornea and include epithelial irregularity, subepithelial and anterior stromal opacities, and punctate posterior stromal opacities located immediately anterior to Descemet membrane.^{10–13} Pre-Descemet corneal dystrophy is characterized by the presence of such posterior stromal opacities thought to represent accumulations of cholesterol sulfate.^{9, 12} Given the infrequency with which ophthalmologists encounter and diagnose this and other disorders associated with dystrophic corneal opacities, we are interested in the utility of molecular genetic analysis to aid the ophthalmologist in the differentiation between dystrophic and non-dystrophic corneal disorders. Therefore, we present a case of an individual with clinical features consistent with pre-Descemet corneal dystrophy and ichthyosis in whom CNV analysis confirmed the diagnosis of X-linked ichthyosis by identifying an Xp22.3 microdeletion containing *STS*.

MATERIALS AND METHODS

The authors followed the tenets of the Declaration of Helsinki in the treatment of the subject reported herein. Study approval was obtained from the Institutional Review Board at The University of California, Los Angeles (UCLA IRB # 11-000020).

After informed consent was obtained, a saliva sample (Oragene saliva collection kits; DNA Genotek, Inc., Ontario, Canada) was collected from the patient and genomic DNA extraction was subsequently performed. The ten exons of *STS* were amplified by polymerase chain reaction (PCR) using the nine primer pairs previously described by Liao et al.¹⁴ Each 25 μ L reaction mixture contained 15.3 μ L deionized water, 2.5 μ L 10x PCR buffer (Sigma-Aldrich, St. Louis, MO), 4.0 μ L of 1.25 mM dNTPs, 2.0 μ L of 25 mM magnesium chloride, 0.2 μ L of each primer (10 μ M), 0.5 μ L of RedTaq genomic DNA polymerase (Sigma-Aldrich, St. Louis, MO), and approximately 30 ng of genomic DNA. The reaction was run in an iCycler Thermocycler (Bio-Rad, Hercules, CA) at 95°C for 3 minutes followed by 25 cycles of 95°C for 3 minutes, 50–68°C gradient for 20 seconds, 72°C for 45 seconds and 72°C for 10 seconds.

A sample of the patient's genomic DNA was submitted to the UCLA Clinical Microarray Core for CNV analysis using aCGH (CytoScanHD array; Affymetrix, Santa Clara, CA). Results were analyzed using the CNV analysis tools within the Partek Genomic Suite Software (Partek Incorporated, St. Louis, MO).

RESULTS

Case Report

A 49-year-old man was referred to one of the authors (AJA) for evaluation of bilateral corneal opacities, first diagnosed approximately 6 years prior. The patient's past medical history was significant for a chronic dermatologic disorder characterized by excessive flaking and scaling, that the patient's 3 brothers and maternal uncle had as well (Figure 1).

External examination revealed thickening and scaling of the skin over the arms and extensor surfaces of the legs consistent with ichthyotic changes (Figure 2). The corrected visual acuities measured 20/15 in the right eye and 20/30 in the left eye, improving with pinhole to 20/25. Slit-lamp biomicroscopic examination of each cornea demonstrated granular grey-white opacities in the posterior corneal stroma that did not involve the peripheral 2–3 mm of each cornea (Figure 3). No corneal endothelial abnormalities were observed and the remainder of the ocular examination in each eye was unremarkable. Specular microscopic imaging of the central corneal endothelium in each eye demonstrated a regular endothelial cell mosaic, with an estimated cell density of 2817 and 2849 cells/mm² in the right and left eyes, respectively.

PCR amplification of each of the 10 exons of *STS* using the patient's genomic DNA failed to generate any amplicons. However, each exon was successfully amplified using genomic DNA from control samples. Additionally, a region of the *ZEB1* gene was successfully amplified using patient and control genomic DNA. As these results were consistent with a deletion of *STS*, CNV analysis was performed, which confirmed an approximately 1.7 megabase deletion in the Xp22.31 region, containing *STS* (Figure 4). In addition, a number of other genes were deleted, including: *VCX3A* (variable charge, X-linked 3A), *RPS27AP17* (ribosomal protein S27a pseudogene 17), *HDHD1* (haloacid dehalogenase-like hydrolase domain containing 1), *MIR4767* (microRNA 4767), *VCX* (variable charge, X-linked), *PNPLA4* (patatin-like phospholipidase domain containing 4), *LOC100506502* (uncharacterized miscellaneous RNA), *MIR651* (microRNA 651) and *VCX2* (variable charge, X-linked 2).

DISCUSSION

Punctate corneal stromal opacities located anterior to Descemet membrane, the most common ocular manifestation associated with XLI, usually appear during early adulthood and are seen in up to 50% of affected male patients and 25% of female carriers.^{6, 9, 15, 16} These opacities were once thought to be invariably present in later life, but subsequent studies have failed to demonstrate an association between age and prevalence of corneal opacities.¹⁷ The stromal opacities typically do not affect vision, although a few cases of affected individuals symptomatic from associated epithelial irregularities, subepithelial stromal opacities and recurrent corneal erosions have been reported.^{11–13, 18–20}

While skin changes in XLI are attributed to a deficiency of the enzyme steroid sulfatase encoded by *STS*, the etiology of the associated corneal changes is still debated. Steroid sulfatase is found throughout the body, including the epidermis, where it is thought to play a role in the steroid production and lipid regulation of the stratum corneum.⁷ As a steroid sulfatase deficiency leads to elevated plasma levels of cholesterol sulfate, the corneal opacities have been postulated to represent focal accumulations of cholesterol sulfate.¹² Electron microscopic examination of a corneal button from an individual with XLI and pre-Descemet corneal dystrophy has revealed electron-dense polymorphic and lamellated material in the posterior corneal stroma anterior to Descemet membrane, suggestive of cholesterol sulfate aggregates.¹² Another hypothesis is that the opacities identified clinically are caused by structural and physiologic changes in stromal tissue indirectly influenced by elevated cholesterol sulfate levels.¹⁵ However, neither theory explains why the characteristic posterior corneal stromal changes do not appear in all individuals with XLI.

To our knowledge, this is the first reported case of pre-Descemet corneal dystrophy associated with X-linked ichthyosis in which the diagnosis was confirmed by identification of a deletion of *STS*. Deletion of a portion of the *STS* coding region has been described in two patients with XLI, although neither of these patients demonstrated any of the ocular

abnormalities associated with XLI, including pre-Descemet corneal dystrophy.^{21, 22} A missense mutation in exon 8 of *STS* has been identified in a female carrier and affected son who both demonstrated “filiform corneal opacities.”²³ To the best of our knowledge, this represents the only point mutation in *STS* associated with pre-Descemet corneal dystrophy and XLI. Although several other *STS* point mutations have been identified in individuals with XLI, these individuals either did not have ocular findings or the reports do not describe an ocular examination.^{23, 24} In the case that we report, the initial diagnosis of XLI and associated pre-Descemet corneal dystrophy was confirmed using CNV analysis after a screening for point mutations in *STS* indicated that the gene was deleted. Thus, aCGH offers ophthalmologists and other clinicians a rapid and relatively inexpensive means to confirm or refute a presumptive clinical diagnosis. Identification of the size of the deletion and the involved genes also provides insight into the basis for the variation in clinical features associated with phenotypically diverse inherited disorders such as XLI.

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Figure 1. Pedigree of family with X-linked ichthyosis. Filled symbols represent affected individuals; open symbols represent unaffected individuals. The proband is indicated by the arrowhead.

Figure 2. Examination of the proband with X-linked ichthyosis demonstrates thickened, dry, scaling skin with characteristic ichthyotic changes on the skin of the lower extremities (a–d).

Figure 3.

Slit lamp examination of both eyes reveals a granular posterior stromal haze (a, right eye). On higher magnification, punctate corneal opacities are noted just anterior to Descemet membrane in the right (b) and left (c) eyes.

Figure 4. Copy number variation analysis demonstrating a deletion on the distal arm of the X-chromosome corresponding to the Xp22.3 locus containing *STS* as well as neighboring genes.