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Clinical features and genetic analysis of two Chinese families with X-linked ichthyosis

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Abstract

Objective: Recessive X-linked ichthyosis (RXLI) caused by deficiency of the steroid sulfatase gene (*STS*) has a reported prevalence of 1/2000 to 1/6000. The present study aimed to characterize the phenotypes and genotypes of two Chinese families with RXLI.

Methods: The patients were referred to the Family Planning Research Institute of Hunan Province for genetic counseling. Their skin phenotypes were photographed, and venous blood was drawn and used for chromosomal microarray analysis (CMA).

Results: The skin phenotype of the proband from the first family was characterized by generalized skin dryness and scaling, with noticeable dark brown, polygonal scales on his trunk and extensor surfaces of his extremities. The proband from the second family had an atypical phenotype showing mild skin dryness over his entire body, slight scaling on his abdomen, and small skin fissures on his arms and legs. No mental disability or developmental anomaly was noted in either proband. CMA revealed that both probands carried a 1.4-Mb deletion on chromosome Xp22.31 involving four Online Mendelian Inheritance in Man-listed genes including *STS*.

Conclusions: Our findings add knowledge to the genotype and phenotype spectrum of RXLI, which may be helpful in genetic counseling and prenatal diagnosis.

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Introduction

Inherited ichthyoses are a group of genetic disorders phenotypically characterized by dry skin, scaling, and hyperkeratosis.[1] According to their clinical features and genetic causes, non-syndromic ichthyoses are classified as common ichthyoses (including ichthyosis vulgaris and recessive X-linked ichthyosis), autosomal recessive congenital ichthyosis, keratinopathic ichthyosis, and other forms.[2,3] As the second most common ichthyosis, recessive X-linked ichthyosis (RXLI) has a reported prevalence of 1/2000 to 1/6000, and mainly affects men.[1] The genetic cause of RXLI is explained by a deficiency of the steroid sulfatase gene (*STS*) on the X chromosome. Complete/partial deletion of the *STS* locus has been detected in 85%–90% patients with RXLI, and the deletion occasionally involves genes adjacent to the *STS* locus.[4–6]

RXLI patients typically exhibit widespread skin dryness and scaling. Dark brown, polygonal scales on the trunk and the extensor surfaces of the extremities are commonly observed,[7] but the phenotype may vary between patients and can resemble that of other forms of ichthyosis.[1] Thus, both clinical and genetic evidence should be collected for the purpose of accurate diagnosis and effective treatment.[8]

Chromosomal microarray analysis (CMA) has been widely used as a first-line test for congenital anomalies, and is capable of detecting microdeletions and duplications within the genome.[9–11] In the present study, we documented the phenotypes of two Chinese families with RXLI and performed CMA.

Materials and methods

Study subjects

The present study was approved by the Medical Ethics Committee of the Family Planning Research Institute of Hunan Province. Two Han Chinese families were enrolled in the study and provided their written informed consent for participation. The proband of the first family was a 28-year-old man who was referred by a dermatology clinic to the Family Planning Research Institute of Hunan Province for genetic counseling. The proband and his maternal uncle provided venous blood samples for CMA. The proband of the second family, a 37-year-old man, was referred with his wife for genetic screening by CMA because of the need for assisted reproduction. The couple has a healthy 7-year-old daughter who was conceived naturally. The parents of this proband also volunteered for CMA. Pedigrees were drawn using HaploPainter software (https://sourceforge.net/).

Physical examination

A physical examination performed by a general physician was offered to both probands, and their skin symptoms were photographed. Neurological and reproductive phenotypes of the probands were evaluated

by specialists in neurology and andrology, respectively.

CMA

Extraction of genomic DNA was performed using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Subsequently, the purified DNA was subjected to digestion, amplification, purification, fragmentation, labeling, hybridization, washing, and scanning according to standard procedures and protocols for the CytoScan HD array (Affymetrix, Santa Clara, CA, USA). Raw data were analyzed using Chromosome Analysis Suite (ChAS) software. Copy number variations of $\geq$100 kb were selected for BLAST analysis. The reference databases used for the present study included DGV (http://dgv.tcag.ca/), DECIPHER (https://decipher.sanger.ac.uk/), Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/), UCSC (https://genome.ucsc.edu/hg19), ISCA (http://www.iscaconsortium.org/), and PubMed. Detailed user guides for both the CytoScan HD array kit and ChAS software are available at https://www.thermofisher.com/.

Results

Proband phenotypes

The 28-year-old proband is from a four-generation family (Figure 1a), and presented with generalized skin dryness and scaling (Figure 2a). Dark brown, polygonal scales were most noticeable on his abdomen (Figure 2b) and the extensor surfaces of his arms and legs (Figure 2c and d). He described his symptoms as usually alleviating during the summer. His maternal uncle (family member II-3) and cousin's sons (family members IV-5, -7, and -9) have congenital ichthyosis, and share similar skin symptoms to the proband.

The 37-year-old proband also belongs to a four-generation family (Figure 1b), and presented with mild skin dryness over his entire body, slight scaling on his abdomen (Figure 3a), and small skin fissures on his arms (Figure 3b) and legs (Figure 3c). He is the only affected member of his family.

Neurological and andrological examinations indicated that neither proband had neurological disorders or cryptorchidism.

Proband genotypes

CMA confirmed a segment loss of 1426 kb on chromosome Xp22.31 (arr[GRCh37] Xp22.31 (6709092_8135568) $\times$ 0) in the 28-year-old proband, which resulted in a deletion of four OMIM genes including *PUDP* (306480), *STS* (300747), *VCX* (300229), and *PNPLA4* (300102) (Figure 4). A 458-kb duplication on Chr14q32.33 was also detected in the 28-year-old proband but this contained no OMIM genes. The maternal uncle (family 1, II-3) of the 28-year-old proband was found to carry a 1685-kb deletion (arr[GRCh37] Xp22.31 (6449752_8135053 $\times$ 0) that involves five OMIM genes including *VCX3A* (300533) and the four aforementioned genes.

A segment loss of 1422 kb on chromosome X (arr[GRCh37] Xp22.31 (6713241_8135053)$\times$0) was identified in the 37-year-old proband, whereas a heterozygous loss of a larger fragment (arr [GRCh37] Xp22.31 (6455149_8135644)$\times$1) was observed in his mother (family 2, II-8). Both the deletions in the 37-year-old proband and his mother affected four OMIM genes including *PUDP* (*HDHD1*), *STS*, *VCX*, and *PNPLA4*. No microdeletions or duplications of $\geq$100 kb were reported in the 37-year-old proband's father (family 2, II-7).

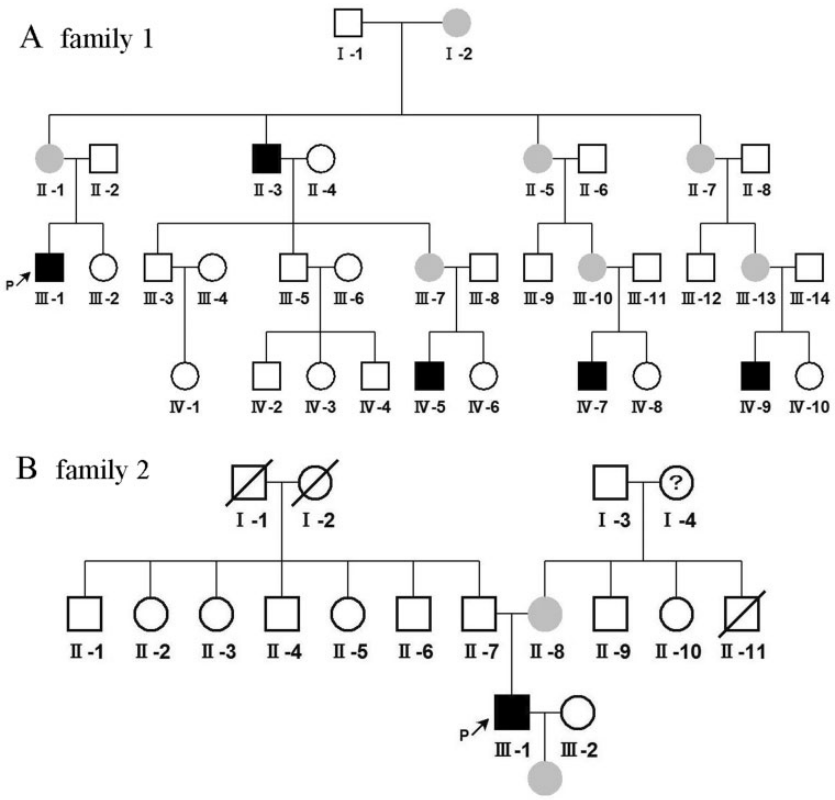

Figure 1. Pedigrees of the two Chinese families with RXLI. Squares and circles indicate males and females, respectively. Squares filled with black represent affected males. Circles filled with grey show the female carriers of pathogenic mutations based on recessive inheritance, and a question mark notes the uncertainty regarding a carrier. A symbol with a diagonal line represents a deceased individual. The proband in each family is shown by an arrow.

Indexed variants

We reasoned that two unrelated patients with RXLI resulting from the same genetic deletions may indicate the presence of a recurrent microdeletion within region Xp22.31. Therefore, we retrieved patient variants from the DECIPHER database using the following filters: 1) the deletion involves *STS*; 2) the documented phenotypes include ichthyosis; and 3) no other microdeletions or duplications are reported for the patient except a microdeletion on chromosome Xp22.31. Among the indexed variants, we focused on those that most closely matched our probands (Table 1). We found that a series of variants of similar size and gene content had been documented. The phenotype of ichthyosis was almost exclusively observed in male patients, supporting the observation that RXLI mainly affects men.

We also found two patients in the database, diagnosed with nonsyndromic inchthyosis, with the same coding gene deletions (*HDHD1*, *STS*, *VCX*, and *PNPLA4*) as the probands in our study. Notably, another patient with the same gene deletions presented with a syndromic phenotype including ichthyosis, a heart abnormality, and intellectual disability.

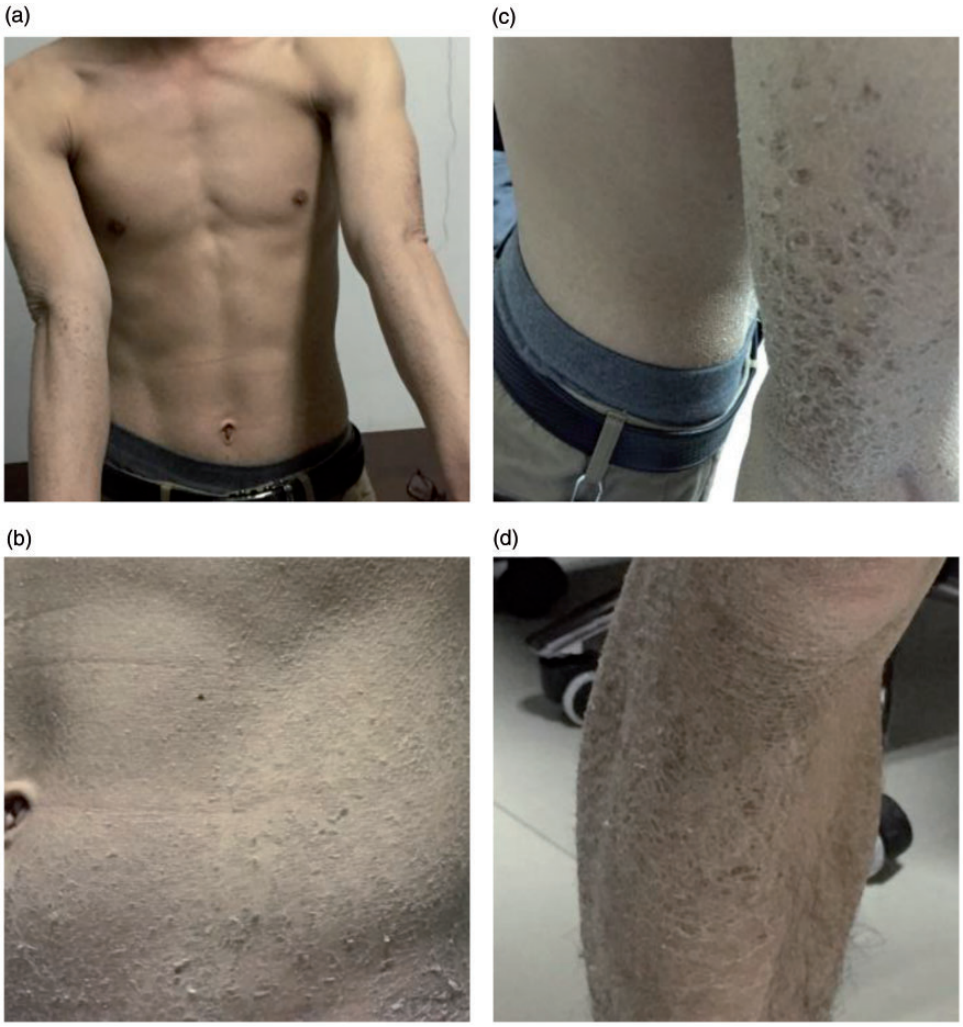

Figure 2. The skin phenotype of the 28-year-old proband in family 1. The proband presented with generalized skin dryness and scaling (a). Dark brown and polygonal scales were visible on his abdomen (b) and the extensor surfaces of his arms (c) and legs (d).

Discussion

The diagnosis of inherited ichthyoses is based on clinical data and genetic results.[8] The clinical features, inheritance pattern, and *STS* deficiency of the 28-year-old proband in the current study together suggested a diagnosis of RXLI. The atypical skin symptoms of the 37-year-old proband provided few clues about RXLI. However, a broad phenotype spectrum of RXLI has been documented,[12] and identification of the *STS* deletion using CMA greatly contributed to his diagnosis. Moreover, CMA revealed that the segment loss in this proband could be traced back at least to his mother who carries a deletion at the same locus.

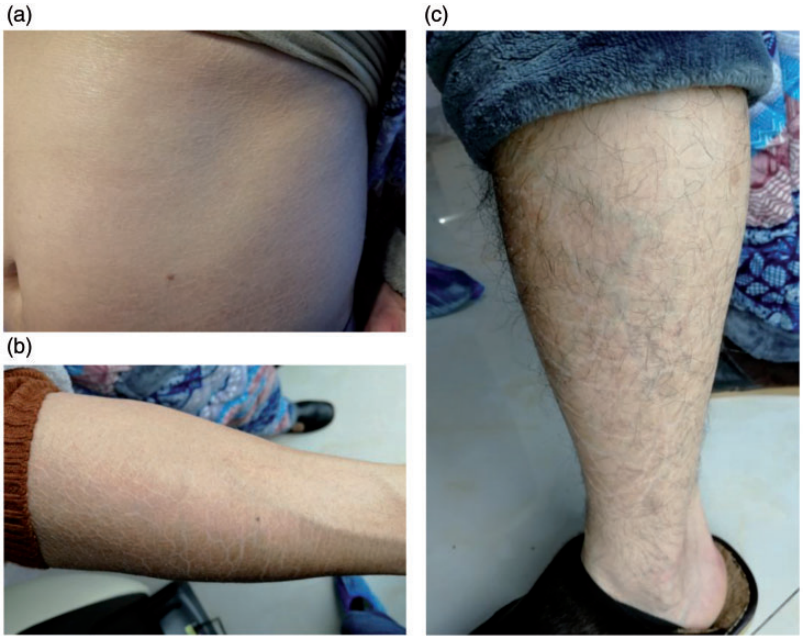

Figure 3. The skin phenotype of the 37-year-old proband in family 2. The proband showed mild skin dryness over the entire body, slight scaling on his abdomen (a), and small skin fissures on his arms (b) and legs (c).

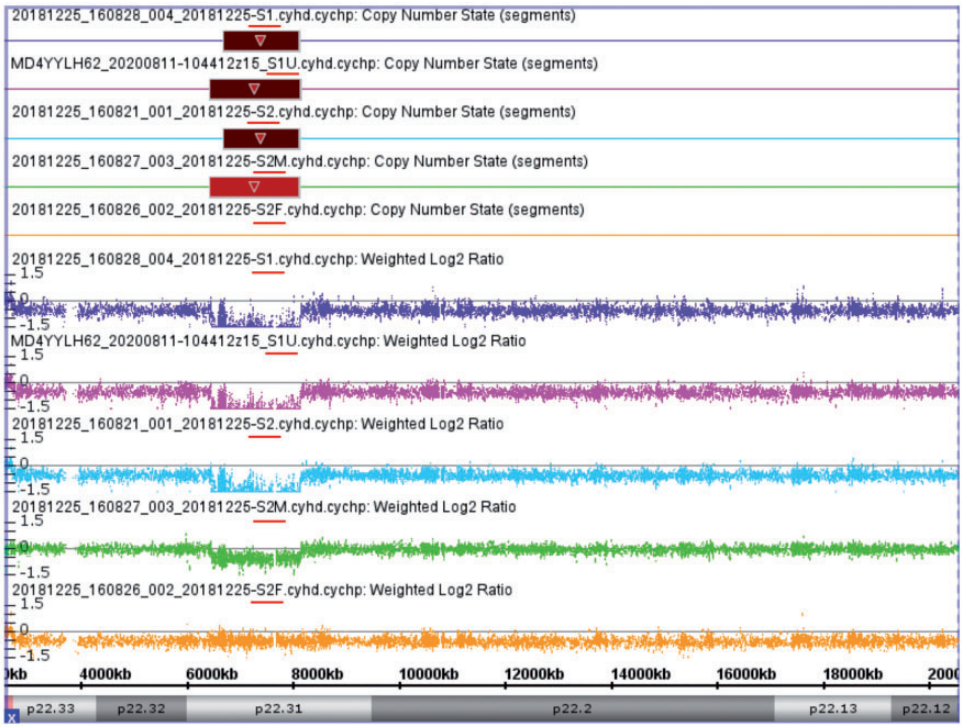

Figure 4. CMA identified segment losses within region Xp22.31 in the probands. Sample S1 and S1U represent the 28-year-old proband and his maternal uncle (II-3), respectively, in family 1. Samples S2, S2M, and S2F correspond to the 37-year-old proband, his mother, and father, respectively, in family 2.

Table 1. Comparison of patient variants from the current study and the DECIPHER database.

Index no.	Variation	Karyotype	Size	OMIM genes	Phenotype(s)	Age*
This report						
Proband 1	[GRCh37] Xp22 (6709092_8135568)×0	46XY	1.42 Mb	HDHD1, PNPLA4, STS, VCX	Ichthyosis	28
Proband 2	[GRCh37] Xp22 (6713241_8135053)×0	46XY	1.42 Mb	HDHD1, PNPLA4, STS, VCX	Ichthyosis, mild	37
DECIPHER						
283235	[GRCh37] Xp22 (7145359_ 7341273)×0	46XY	195.91 kb	STS	Ichthyosis; intellectual disability, moderate	7
350438	[GRCh37] Xp22 (7073279_ 7744191)×0	46XY	670.91 kb	STS	Ichthyosis; intellectual disability, mild	3
350318	[GRCh37] Xp22 (6489877_ 8107259)×0	46XY	1.62 Mb	HDHD1, PNPLA4, STS, VCX	Abnormal heart morphology; ichthyosis; intellectual disability	14
326575	[GRCh37] Xp22 (6467006_ 8131810)×0	46XY	1.66 Mb	HDHD1, PNPLA4, STS, VCX	Congenital ichthyosiform erythroderma	6
327577	[GRCh37] Xp22 (6516735_ 8131442)×0	46XY	1.61 Mb	HDHD1, PNPLA4, STS, VCX	Atopic dermatitis; ichthyosis	/
270877	[GRCh37] Xp22 (6452685_ 7960088)×0	46XY	1.51 Mb	HDHD1, PNPLA4, STS, VCX, VCX3A	Ichthyosis	57
267969	[GRCh37] Xp22 (6442119_ 7922342)×0	46XY	1.48 Mb	HDHD1, PNPLA4, STS, VCX, VCX3A	Feeding difficulties in infancy; ichthyosis; dysarthria; short attention span	4
411523	[GRCh37] Xp22 (6552712_ 8115153)×0	46XY	1.56 Mb	HDHD1, PNPLA4, STS, VCX, VCX3A	Ichthyosis; diabetes mellitus	10

"*", age (years) at last clinical assessment; "/", information is not available.

CMA has been widely used as a first-line test for inherited diseases.[13] However, the identification of missense/nonsense mutations and small indel mutations responsible for the *STS* deficiency are beyond its current detection limits.[14,15] Next-generation sequencing, such as whole exome sequencing, is a more sensitive technique that can be used to accurately identify a pathogenic mutation.[16]

A previous study showed that men whose *STS* deletions were identified using CMA tended to have milder skin phenotypes compared with those diagnosed with typical XLI in dermatology clinics.[12] Our current observations are in line with this, in that the phenotype of the 37-year-old proband incidentally identified with an *STS* deletion was atypical compared with that of the 28-year-old proband who was diagnosed in a dermatology clinic.

Although there may be linkage between certain symptoms (such as intellectual disability or autism) and the size and gene content of the deleted fragment, there is currently no evidence for a general genotype–phenotype correlation for X-linked ichthyosis.[12] The comparison of genotypes and phenotypes of the patients in the current study and similar cases in the database also supports this conclusion (Table 1). Previous observations concluded that the deletion of *VCX3A* was not sufficient to cause mental retardation in patients with X-linked ichthyosis.[17,18] This is also supported by our patients and those documented in the database (Table 1). Of note, patients with deletions that only affect *STS* may also have a syndromic phenotype (Table 1). The most recent retrospective review of a case series highlighted the high prevalence of neurological disorders in RXLI.[19]Thus, in addition to examining skin symptoms, clinicians should be aware of cryptic neurological disorders to make a comprehensive and accurate diagnosis.

In summary, our study implies that the diagnosis of RXLI with atypical phenotypes requires caution, and should be made on the basis of both clinical and genetic analyses.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of the Family Planning Research Institute of Hunan Province. All study subjects provided written informed consent to participate in the study.

Consent for publication

The study subjects provided written informed consent for the publication of any associated data and accompanying images.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

W.Q.X. analyzed the data and wrote the manuscript, H.Y.Z., L.Z., Y.G., and J.W.L performed the experiments, and Y.C. recruited the participants and designed the study.

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