

SHORT COMMUNICATION

A Case of Syndromic X-linked Ichthyosis with Léri-Weill Dyschondrosteosis

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Léri-Weill dyschondrosteosis (LWD) is a skeletal dysplasia marked by disproportionate short stature and characteristic Madelung wrist deformity, which is an epiphyseal growth plate disturbance characterized by dorsal and radial bowing of the radius. In approximately 70% of cases, LWD is caused by haploinsufficiency of the short stature homeobox (*SHOX*) gene, which maps to the pseudoautosomal region 1 (PAR1) of the sexual chromosomes (Xp22.33 and Yp11.32). Haploinsufficiency results from heterozygous mutations and deletions of *SHOX* or the downstream PAR1 (where *SHOX* enhancer elements are located). The molecular defect remains unknown in the other 30% of LWD cases. X-linked ichthyosis (XLI) is the second most common type of ichthyosis, with a prevalence of 1/6,000. The condition is an X-linked recessive disorder of cutaneous keratinization caused by a deficiency in steroid sulfatase (STS) activity. STS is thought to play a role in active cutaneous steroid production and lipid regulation. The gene coding for STS has been mapped to the short arm of the X chromosome at Xp22.3. When accompanied by associated manifestations, such as testicular maldescent, XLI is regarded as syndromic.

We report here a case of a 16-year-old French male who sought dermatology consultation for xerosis and skin with a dirty appearance. He benefited from growth hormone for LWD due to *SHOX* haploinsufficiency. We diagnosed ichthyosis due to STS deficiency in this patient. A contiguous gene deletion syndrome involving *SHOX* and STS was suspected. Contiguous genes syndromes manifest complex phenotypes that result from the co-deletion of adjacent genes.

CASE REPORT

A 16-year-old patient was administered growth hormone for 2 years for short stature due to LWD. His mother was also affected by the disease and presented with short stature and Madelung deformity. His mother reported wide desquamation in her son shortly after birth. The patient also presented with left cryptorchidism. His disproportionate short stature and Madelung deformity were characteristic of LWD. The disease was confirmed by fluorescence *in situ* hybridization (FISH) analysis, which revealed a *SHOX* deletion. FISH analysis for *SHOX* in the mother also revealed *SHOX* deletion, whereas no abnormality was observed in the patient's father. Hormonal testing did not reveal hypogonadotropic hypogonadism. Olfactory testing was normal. At-

tention deficit hyperactivity disorder (ADHP) was suspected initially, but only the patient's depression, which was probably related to the disease as well as his short stature and skin appearance, was evident after hospitalization.

At the dermatology consultation, he presented with dark-brown scales on the extensor surfaces and a dirty appearance of the neck. Grey polygonal scales predominated on the lower limbs. Flexures were affected, but the palms, soles, hairs and nails were spared. An X-linked ichthyosis (XLI) was suspected.

Given the associated abnormalities, a contiguous gene syndrome caused by a deletion in Xp was suspected and appropriate additional investigations were initiated.

Analysis revealed a deletion of 28 contiguous probes (09333_L10292 to 05587_L04577), which includes the *SHOX* gene, its regulatory region and *NLGN4X* at Xp22.32. The centromeric breakpoint was within a range of 2.3 Mb between these gene and *KAL1*, which was not deleted. *STS* and *VCX3A* deletions were observed with real-time quantitative PCR (Fig. 1).

MATERIALS AND METHODS (see Appendix S1¹).

DISCUSSION

The distal region of the short arm of the X-chromosome has a particularly high frequency of interstitial deletions. In males, large deletions involving Xp22 cause contiguous gene syndromes with highly variable symptoms that depend on the genes encompassed by the deletion. Xp22.3 deletions in males can be associated with LWD (OMIM 127300) (3) and some cases of short stature (*SHOX*) (4), chondrodysplasia punctate (*ARSE*) (5), mental retardation (*VCX-3A* gene at the MRX49 locus) (6), ichthyosis (*STS*) (7–9), Kallman syndrome (*KAL1*) (8) and ocular albinism (*OAI*) (10). Of these genes, only *SHOX* resides within the pseudoautosomal region (PAR1) (11) and is identical on both

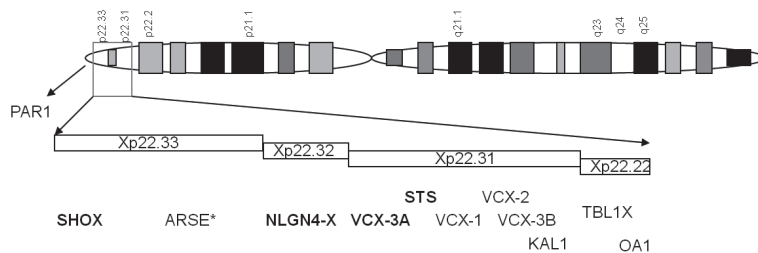


Fig. 1. Map showing the genes of interest in the Xp22.33–Xp22.22 region. Genes deleted in the patient are shown in bold. **ARSE* gene was not studied.

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2356>

the X and Y chromosomes. The remaining 5 genes are X-chromosome specific and inherited as X-linked recessive traits.

Our patient presented with XLI and LWD related to a Xp22.3 deletion inherited from his mother and involving *STS* and *SHOX*, respectively. These 2 genes are separated by several megabases. A contiguous deletion encompassing the *SHOX*, *ARSE*, *NLGN4X*, *VCX3A* and *STS* genes could explain the clinical features. Unfortunately, the *ARSE* deletion was not studied. Two distinct deletions are also potentially involved.

The patient benefited from growth hormone for LWD for 2 years, but ichthyosis was not previously diagnosed. He experienced a significantly reduced quality of life with consequences on his social interactions due to ichthyosis. Indeed, Dermatology Life Quality Index (DLQI) is significantly reduced among ichthyosis patients, as demonstrated by Gånemo et al. (11). The ichthyosis diagnosis allowed the patient to feel better by improving his acceptance of his skin, and he lost his feelings of guilt about being dirty.

Previous data suggest that *VCX3A* gene deletions are responsible for mental retardation in patients with X-linked ichthyosis (2, 6). However, Cuevas-Covarrubias & Gonzalez Huerta published data suggesting *VCX3A* gene deletions in XLI patients with normal intelligence (12). The authors indicate that more complex mechanisms in association with epigenetic and/or environmental factors are potentially implicated in the genesis of mental retardation in X-linked ichthyosis. A *VCX3A* gene deletion was detected in our patient, who was enrolled in general and vocational education programmes because of mild learning disabilities without obvious mental retardation.

Given the discovery of a nonsense mutation in *NLGN4X* in 2 autistic brothers, *NLGN4X* is thought to be essential for communication processes (13). This gene was also deleted in our patient, who presented with depression that necessitated hospitalization in a psychiatric department. The depression was considered secondary to his small stature and did not necessitate medication. The diagnosis of a skin disease was very helpful because it meant that he was not dirty and that treatment was possible. In our case, the role of the *NLGN4X* deletion in the development of depression is impossible to assert. Mochel et al. (14) reported a patient with strictly normal intelligence and social interactions despite severe ichthyosis and Kallman syndrome linked to a contiguous deletion of *NLGN4X* and the *VCX* genes.

In conclusion, we report here a case of LWD and XLI related to a Xp22.3 deletion. Dermatologists and paediatricians must be aware of contiguous genes in order to detect the other abnormalities linked to the deletion of genes adjacent to *STS*. This case illustrates the complexity of interpreting the neurobehavioural phenotypes of male patients with Xp22.3 deletions.

These syndromes offer rare, but valuable, opportunities to assign genes to human phenotypes or biological processes and must be identified.

The authors declare no conflicts of interest.

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