X-linked spondyloepiphyseal dysplasia tarda

Molecular cause of a heritable disorder associated with early degenerative joint disease

Jörg Fiedler[1], Carsten Bergmann[2] and Rolf E Brenner[1]

[1]University of Ulm, Department of Orthopedics, Division for Biochemistry of Joint and Connective Tissue Disorders, RKU, Oberer Eselsberg 45, DE-89081 Ulm, [2]Aachen University of Technology, Institute of Human Genetics, Germany
Correspondence: rolf.brenner@medizin.uni-ulm.de
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ABSTRACT **Spondyloepiphyseal dysplasia tarda (SEDT) is a genetically heterogeneous disorder often associated with the early onset of osteoarthrosis. The X-linked recessive form (SEDL) affects men and is characterized by reduced height, arm span exceeding total height, and barrel chest deformity. The radiographic phenotype comprises a hump-shaped deformity of vertebral bodies and mild epiphyseal dysplasia of the femoral head associated with early signs of hip arthrosis. The disorder is caused by mutations in the SEDL (or sedlin) gene on Xp22.12-p22.31. In 4 male patients from a German family, we identified a new nonsense mutation in SEDL exon 4 (C74A). The carrier status for the mutation could be confirmed in 2 women of the family, both of whom show no obvious signs of bone and joint diseases. SEDT should be kept in mind as a differential diagnosis in men with early "primary" bilateral osteoarthrosis.**

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The term spondyloepiphyseal dysplasia (SED) comprises a heterogeneous group of disorders, which share radiographic abnormalities of the vertebral bodies and epiphyseal regions. Short stature and early development of degenerative joint disease are frequent additional features. SED has been divided into a severe congenita and a more benign tarda form reflecting the broad range of clinical severity. It is genetically heterogeneous and is associated with autosomal dominant, autosomal recessive, or X-linked recessive modes of inheritance. Collagen type II, the most abundant collagen of cartilage, is mutated in autosomal dominant forms of SED (Spranger et al. 1994) or spondyloepimetaphyseal dysplasia (SEMD) Strudwick type (Tiller et al. 1995). Since collagen type II is also a component of the vitreous humor, these patients may have additional ophthalmological problems, like severe myopia and/or retinal detachment. A rare autosomal recessive form of SED associated with insulin-dependent diabetes mellitus (Wolcott-Rallison-syndrome) has recently been attributed to mutations in the translation factor EIF2AK3 (Delepine et al. 2000). In another autosomal recessive form of SEMD, mutations have been described in the ATPSK2 gene that is involved in sulfate activation (ul Haque et al. 1998).

X-linked spondyloepiphyseal dysplasia tarda (SEDL) is a mild variant with moderately short stature, barrel chest deformity and minor epiphyseal, but characteristic, vertebral body dysplasia comprising platyspondyly and a central hump (Iceton and Horne 1986, Whyte et al. 1999). Degenerative joint disease is common in male patients and often makes hip replacement necessary in the fourth or fifth decade. In 1988, the gene responsible for SEDL was mapped to Xp22 (Szpiro-Tapia et al. 1988). Recently, several mutations in a gene located in that region have been described in patients with SEDL (Gedeon et al. 1999, Whyte et al. 1999, Mumm et al. 2000, Gedeon et al. 2001, Grunebaum et al. 2001, Mumm et al. 2001, Tiller et al. 2001). This gene,

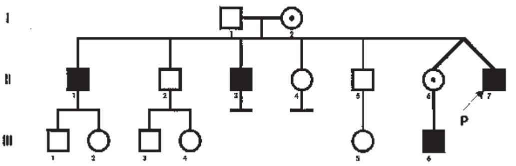

Figure 1. Pedigree of the described family with X-linked spondyloepiphyseal dysplasia tarda.

termed SEDL, is expressed in cartilage and various other tissues (Gecz et al. 2000). Thus, mutation screening offers a new diagnostic tool for a subset of men who have early degenerative joint disease and additional features of SEDL. Here we present a family in whom we identified a new nonsense mutation in the SEDL gene.

Patients and methods

FamÕy report

The index patient II-7 was seen at the age of 37 years with painful spine and hip joints. Radiographic evaluation showed degenerative changes of both hip joints, including joint space narrowing and subchondral sclerosis with mild signs of epiphyseal and vertebral body dysplasia. The family history revealed 3 other men (II-1, II-3, and III-6) who were similarly affected. The family's pedigree indicated an X-linked recessive type of inheritance (Figure 1) with two women (I-2 and II-6) suspected of being carriers of the mutant allele. Detailed clinical and anthropometric data and blood samples were taken from all patients and the presumptive two female carriers after informed consent had been given.

MutatŠn analysis

For mutational screening, all 6 exons of the SEDL gene (4 of which are translated) were analyzed by primer cycle sequencing. Genomic DNA was isolated from blood samples with QIAmp(r) DNA Blood Mini Kit (QIAGEN, Hilden, Germany) in accordance with the manufacturer's instructions. The amplification, primers, and PCR conditions are described elsewhere (MacKenzie et al. 1996, Gedeon et al. 1999). Sequencing was done by using the Thermo Sequenase Primer Cycle Sequencing Kit. The samples were run on a fluorescent automated DNA sequencer ALFexpress and data processing was done by using the ALFwin Sequence Analyzer Software V2.1 (all Amersham Biosciences Europe GmbH, Freiburg, Germany).

Results

Clinical phenotype

All affected patients had a barrel chest deformity and their height was at the lower extreme of the normal range (adult height between 160 and 168 cm). The height of their 2 healthy adult brothers (III-2 and II-2) was 182 and 185 cm, indicating an intrafamiliar reduction of about 20 cm caused by the disease. All patients showed an arm span exceeding their total height by 11–16 cm, reflecting a disproportion between rump and limb length (Figure 2). From the end of the first decade, all patients have had backache and pain in their weight-bearing joints (Table). One (II-3) also had a history of lumbar vertebral disc herniation. The patients showed radiographic evidence of early degenerative joint disease of the hips, including

Clinical data of affected family members and female carriers

	Age (years)	Height (cm)	Arm span (cm)	Barrel chest	Joint pain	Osteoarthrosis	Additional features
Patient no.							
III-6	12	147	163	Yes	Spine	No	
II-7	37	161	176	Yes	Spine, hips	Hips	
II-3	41	168	179	Yes	Spine, hips, knees	Hips, knees	Lumbar disc protrusion
II-1	47	160	174	Yes	Spine, hips, knees, ankles	Hips, knees	
Carrier no.							
II-6	38	173	169	No	No	No	
I-2	68	164	163	No	Knees	Knees	Osteoporosis

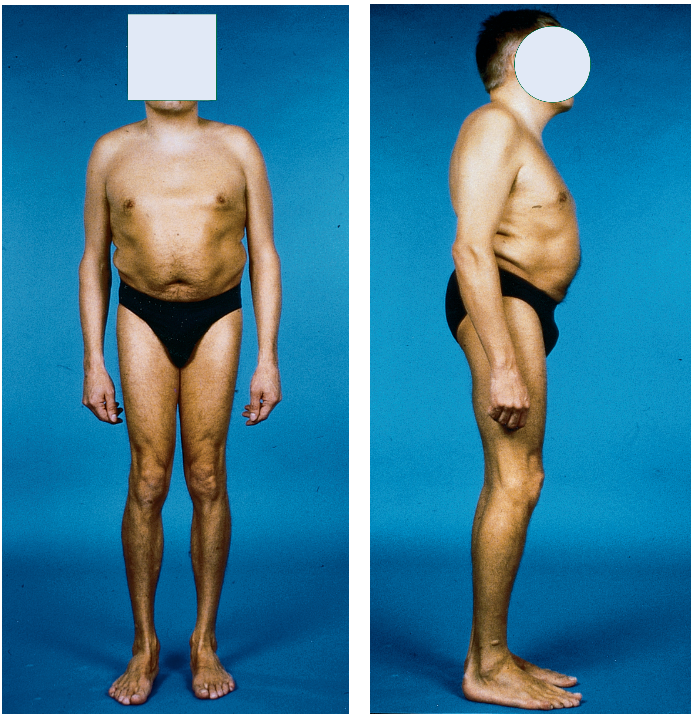

Figure 2. 41-year-old man with barrel chest deformity and disproportion between length of the rump and limbs (front and side views).

subchondral sclerosis, irregularities, and narrowing of the joint space or small cystic lesions in the subchondral bone (Figure 3 A, B). The radiographs of the lumbar spine showed dysplasia of the vertebral bodies with a more or less marked hump in the central or dorsal region (Figure 3 C, D).

The two female carriers (I-2 and II-6) had no disproportion, their height and arm span being nearly equal. Their height was 173 cm and 164 cm at an age of 38 years and 68 years, respectively. The older female carrier had recurrent knee pain and a history of osteoporosis, while the younger one had no complaints related to her skeletal system.

MutatŠn analysis

Direct sequencing of PCR-amplified SEDL-exons 1–6 with their flanking regions revealed hemizygosity for a point mutation in the index patient II-7. This mutation affects nucleotide position 74 of exon 4 and changes the codon for the amino acid serine (TCG) to a stop codon (TAG) (Figure 4 A). Segregation of the mutant allele was confirmed by sequence analysis in all affected family members and the two female carriers (Figure 4 B). No changes in other regions of the SEDL-gene were detected.

Discussion

As shown in the present family, the phenotype of X-linked spondyloepiphyseal dysplasia tarda is not impressive at an early age. Later in life, there is an overlap with degenerative disease of weightbearing joints and the spine (MacKenzie et al. 1996, Whyte et al. 1999). Moroever, an X-linked recessive mode of inheritance may interfere with identification of its heritable basis. Therefore, some cases may not be recognized during routine orthopedic care and the incidence of SEDL patients may be higher than expected so far. Especially males with early “primary” degenerative joint disease of the hips, chronic back pain, disproportion of rump and limb length and a positive family history should be evaluated. If this additional information supports the diagnosis of SEDL, radiographs should be taken of the lumbar spine.

Hitherto, 21 different mutations have been identified in patients with X-linked spondyloepiphyseal dysplasia (MacKenzie et al. 1996, Gedeon et al. 1999, Whyte et al. 1999, Mumm et al. 2000, Gedeon et al. 2001, Grunebaum et al. 2001, Tiller et al. 2001). These mutations are spread over the gene’s entire coding region comprising exons 3–6; however, mutational “hotspots” are exon 4 and 5. The most frequent genetic defects found in SEDL patients are nonsense mutations, splice site mutations, deletions and insertions. The mutation identified in the present study has not been described before. It directly creates a stop codon in exon 4. This type of mutation has previously been reported regarding 2 other nucleotide positions in exon 4 and exon 5. As yet, there is no clear genotype-phenotype correlation indicating that major parts of the gene have functional importance and that the whole gene product may be necessary for

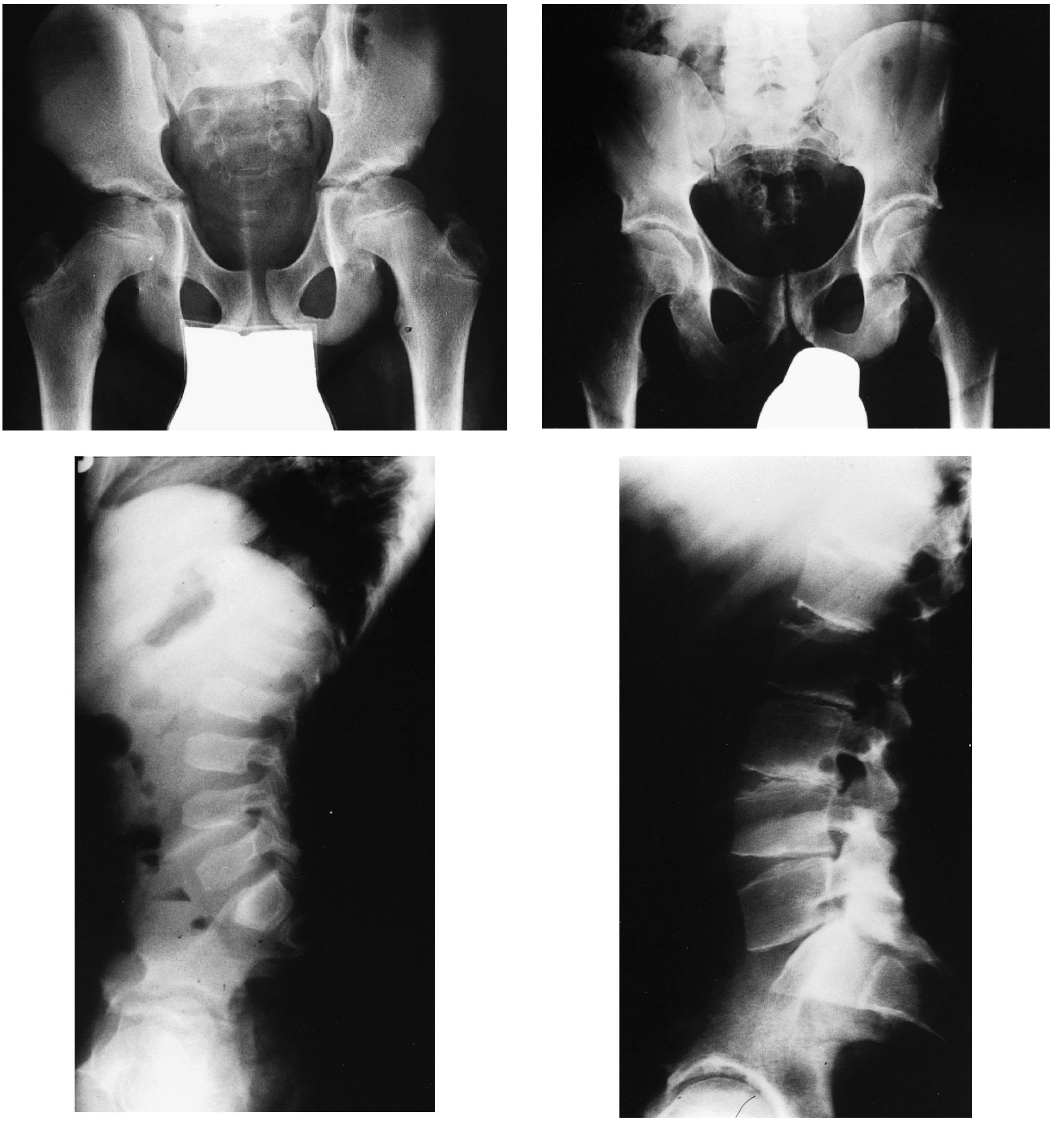

Figure 3. The hip joints and the lumbar spine of two affected male family members at the age of 12 (left) and 41 (right) years, respectively.

functional integrity of the translated protein. The precise function of the SEDL protein is not known. It has been suggested that it is involved in intracellular transport processes of molecules, which may be of special importance for cartilage since chondrocytes need a high synthetic capacity for extracellular matrix molecules. Moreover, the association with early development of osteoarthrosis may depend in part on a quantitatively reduced biosynthesis of extracellular matrix molecules. Therefore, a more detailed investigation of X-linked spondyloepiphyseal dysplasia may lead to a novel pathogenetic model for the early development of osteoarthritis.

Female carriers heterozygous for a mutation in the SEDL-gene reported hitherto had either minor radiographic abnormalities of the knees, narrowing of the intervertebral disc space and spurring (Mumm et al. 2000) or no objective changes (Grunebaum et al. 2001). The observed differences may depend on the type of the underlying molecular defect and the resulting residual function of the

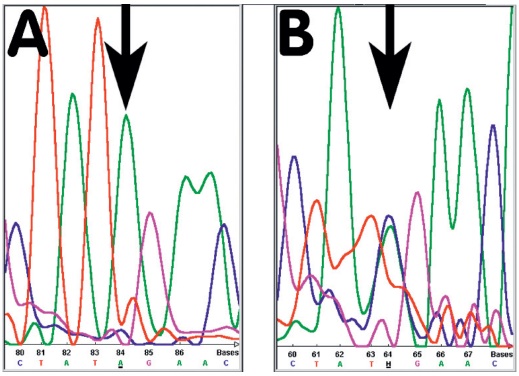

Figure 4. Sequence analysis in one male patient (A) and one female carrier (B) showing hemizygosity (A) and heterozygosity (B) for the point mutation (C/A) at nucleotide position 74 of exon 4 of the SEDL-gene. This mutation converts the codon for the amino acid serine (TCG) to a stop codon (TAG).

SEDL-protein. Recurrent knee pain and low-grade osteoarthritis of the 68-year-old female carrier in our family fit well into that model because the defect identified is supposed to cause a premature stop of translation. Osteoporosis, which has been diagnosed previously in that female carrier, has not been associated with SEDL as yet. Therefore, it seems unlikely that it is related to heterozygosity for the SEDL-mutation.

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No competing interests declared.

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