European Journal of Human Genetics (2003) 11, 639–642

www.nature.com/ejhg

PRACTICAL GENETICS

Spondyloepiphyseal dysplasia tarda (*SEDL*, MIM #313400)

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Spondyloepiphyseal dsplasia tarda (SEDL) is a radiologically distinct, X-chromosome linked primary skeletal dysplasia characterised by disproportionate short-trunked short stature, dysplasia of the large joints (hip) and flattened thoracic and lumber vertebral bodies. Molecular basis for SEDL has been elucidated by the identification of various mutations (currently >30) in the *SEDL* gene from Xp22 region. The function of the SEDL protein is not known although it is speculated that it may participate in the ER-to-Golgi transport as part of a novel highly conserved multiprotein TRAPP complex.
European Journal of Human Genetics (2003) **11,** 639–642. doi:10.1038/sj.ejhg.5201025

Keywords: spondyloepiphyseal dysplasia tarda; bone dysplasia; X-linked; TRAPP

Clinical definition

Spondyloepiphyseal dysplasia tarda (SEDL) is a well-defined, X-linked primary skeletal dysplasia that predominantly affects the spinal vertebral bodies and epiphyses during skeletal growth.[1] The condition is not evident at birth, the usual age of presentation being after the first decade of life. Disproportionate (short-trunked) short stature in a male, with or without back pain, is the common presenting feature. Other characteristic clinical features include a broad chest with mild sternal protrusion and limitation of joint motion at the hips and elbows.[2] Craniofacial appearance, vision, hearing and intelligence are unaffected in SEDL and there are no consistently associated extraskeletal anomalies. The radiographic manifestations of SEDL are diagnostic, clearly distinguishing it from other conditions that it has most recently been grouped together within the current classification[3] (see Table 1). The most characteristic of these is seen in the lateral view of the thoraco-lumbar spine; comprising generalised platyspondyly, narrowing of intervertebral disc spaces, and pathognomonic superior and inferior 'humps' involving the posterior two-thirds of the flattened vertebral bodies[2] (see Figure 1). These changes are best appreciated in late childhood and adolescence, and may become superimposed by secondary arthritic changes in later decades. The major potential medical complication of the disorder is premature arthritis, predominantly affecting the spine and hip joints.[1] Hip joint disease may be severe, necessitating replacement in early adult life.[1] There is a wide range of inter- and intrafamilial variability among affected males in regard to severity of disease. Females have also been reported with classic radiographic features of *SEDL*,[4] but this occurrence is rare, if not unique, and in such females mutations in the *SEDL* gene are yet to be identified.

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Received 20 December 2002; revised 17 March 2003; accepted 1 April 2003

Diagnosis

Diagnosis is suggested by the presence of disproportionate (short-trunk) short stature in a male (typically aged 8–15

Table 1 Current classification of the spondyloepiphyseal dysplasias and related disorders

	Mode of inheritance	*OMIM syndrome*	*Chromosome locus*	*Gene*	*Protein*	*OMIM gene/protein*
X-linked SED tarda	XL	313400	Xp22.2–p22.1	SEDL	SEDLIN	300202
SEMD Handigodu type	AD					
Progressive pseudorheumatoid dysplasia	AR	208230	6q22–q23	WISP3		603400
Dyggve–Melchior–Clausen dysplasia	AR	223800	18q21.1			
Wolcott–Rallison dysplasia	AR	226980	2p12	EIF2AK3	transcription factor	604032
Immunoosseous dysplasia (Schimke)	AR	242900	2q35	*SMARCAL1*	Transcription factor	606622
Schwartz–Jampel syndrome	AR	255800	1q36–34	*PLC* (*HSPG2*)	Perlecan	142461
SEMD with joint laxity (SEMDJL)	AR	271640				
SEMD with dislocations (Hall) (leptodactylic type)						
Sponastrime dysplasia	AR	271510				
SEMD short limb – abnormal calcification type	AR	271665				
SEMD Pakistani type	AR	603005	10q23–24	PAPSS2	PAPSS2	603005

years) and confirmed by the characteristic vertebral morphology on a lateral radiograph of the thoraco-lumbar spine. Full radiographic survey of the skeleton may also reveal small and irregular epiphyses in childhood and evidence of osteoarthritic change in later life. The most important diagnostic 'tools' are a three-generation family history (suggestive of X-linked inheritance) and radiographic skeletal survey. Diagnosis can now also be verified by the finding of a mutation in the *SEDL* gene.

Differential diagnosis

SEDL is readily differentiated from the other currently classified (Table 1) spondyloepiphyseal dysplasias by age of onset, pedigree analysis and the above radiographic findings on lateral spinal radiographs. There are other late-onset spondyloepiphyseal dysplasias that are not well characterised, but none of these have the typical vertebral morphology change seen in *SEDL,* and many have other differentiating clinical findings. Perhaps the most common reason for not finding a *SEDL* mutation in an 'affected' male is misdiagnosis.

Gene

The *SEDL* gene was identified by the screening of positional candidate genes from within a minimal ~170 kb interval in Xp22 refined by linkage mapping on two families segregating *SEDL*.[5] It is a small gene, which escapes X-inactivation, composed of six exons spanning 20 kb of genomic DNA. Ubiquitously expressed *SEDL* mRNA is about 2.8 kb in size. It is alternatively spliced involving exons 2, 4 and 6. *SEDL* coding region of 420 bp is split among exons 3–6. Exons 1 and 2 are noncoding. Exon 2 contains a MER20 repetitive sequence and there are four *Alu* repeats within the 3′ untranslated region. *SEDL* gene is a highly conserved gene with orthologs identified in yeast, fly and vertebrates.[5]

Pseudogenes

SEDL gene has at least seven pseudogenes in the human genome: one *SEDLP1* on chromosome 19q13.4; one *SEDLP2* on chromosome 8q13.3; and five *SEDLP3-SEDLP7*, pseudogenes on chromosome Yq11.23.[6] While *SEDLP1* and *SEDLP2* are processed pseudogenes generated by retrotransposition, the Y-chromosome-bound pseudogenes arose by duplication. Interestingly, the chromosome 19 pseudogene, *SEDLP1* is transcribed (ubiquitously) from a novel promoter and encodes for a protein, which would be 100% identical to that of the *SEDL* gene. It still remains to be determined whether the *SEDLP1* mRNA of 0.75 kb is translated. There are only six silent nucleotide differences between the open reading frame of the *SEDL* gene and the *SEDLP1* pseudogene. Other *SEDL* pseudogenes are not transcribed.[6]

Genetic heterogeneity

Although X-linked *SEDL* can be distinguished from the other currently classified spondyloepiphyseal dysplasias by typical radiographic findings, not all such patients have *SEDL* gene mutations identified (15% or six cases with clinically defined isolated *SEDL* were negative when tested for *SEDL* gene mutations).[7] This may indicate some genetic heterogeneity of *SEDL*, although complete skeletal surveys of these six cases were not available for review.

Function of the protein

SEDL gene open reading frame of 420 bp encodes a small protein of 140 amino acids. It does not show similarity to any known proteins and there are no conserved protein domains detected. Human recombinant *SEDL* protein localised to perinuclear membrane structures which partly overlap with VTC (vesicular tubular compartment, known

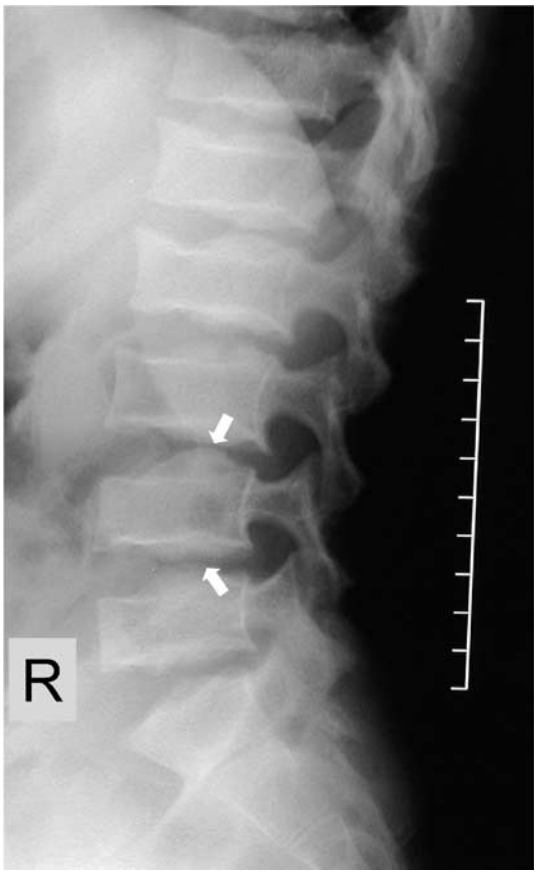

Figure 1 Lateral radiograph of the lumbo-sacral spine in a 15-year-old male with SEDL. Note diagnostic features of platyspondyly with superior and inferior bony 'humps' affecting the middle and posterior thirds of the vertebrae (arrowheads).

also as ERGIC – ER-to-Golgi intermediate compartment) pointing towards the role of *SEDL* protein in vesicular transport between ER and the Golgi.[6] This function is further supported by studies of the *SEDL* yeast ortholog, *YBR254C* (or its protein TRS20). TRS20 is a member of a novel multiprotein complex called transport protein particle (TRAPP) which mediates vesicle docking and fusion.[8] Yeast *YBR254C* knockout experiments show that the yeast *SEDL* ortholog function is essential for the yeast cell.[9] This is not the case for the human *SEDL*, where patients lacking entire *SEDL* gene survive (see below). More recently, crystal structure of the human SEDL protein has been determined. This revealed an unexpected similarity to the structures of the *N*-terminal domain of two SNAREs (soluble *N*-ethylmaleimide-sensitive factor attachment
receptor proteins), Ykt6p and Sec22b, despite no sequence similarity between these proteins and *SEDL*. A regulatory and/or adaptor role of SEDL protein through multiple protein–protein interactions is proposed.[10]

Yeast model

There is no animal model for *SEDL* available however, there is a yeast model. The yeast *YBR254C* knockout is not viable.[9] Preliminary results of complementation experiments with human recombinant *SEDL* protein show that the human *SEDL* protein is able to rescue the lethal *YBR254C* KO phenotype and thus TRS20 protein function (J Gécz, unpublished data).

Mutations

To date 30 different *SEDL* gene mutations have been identified in 40 unrelated cases. In addition to 21 previously summarised mutations,[7] nine have recently been described. These include four new deletions, intron5/exon6del(1371–1445 bp) and intron5/exon6del(750 bp),[11] intron2/exon3del[12] and 267-271delAAGAC,[13] one missense mutation, T248C,[14] and four nonsense mutations, G210A and C364T,[11] C391T,[15] and C329A.[16] The most common mutations identified are deletions, accounting for 50% of the types of mutations identified (15/30). The splice site mutation IVS3+5G>A is the most frequently found *SEDL* mutation to date with five patients identified. *SEDL* gene mutations are spread along the entire length of the four *SEDL* coding exons and their flanking introns, that is, exons 3–6. As yet there are no mutations reported in the untranslated exons 1 and 2. There is no obvious correlation between the nature of the mutation and the clinical severity of SEDL. All identified so far mutations *SEDL* gene appear to have the same effect, loss of function of the SEDL protein, irrespective of their location and type (null mutations, small or large deletions, splice site mutations and missense mutations).

Given the small number of *SEDL* gene exons and the relative ease of their PCR amplification, direct sequencing is the method of choice for *SEDL* mutation detection. Primers, which specifically amplify only the X-chromosome gene sequences, have been described.[5]

Treatment

There is no specific treatment apart from management of the complications of the condition. The most common of these is management of hip dysplasia, which may require hip replacement. Advice should be given regarding prevention of premature arthritis by maintenance of a healthy weight for height and also regular, low-impact exercise such as swimming and cycling. Data regarding the use of the growth hormone in this condition and its effect on final adult height are not available. Significant short stature is usual in this condition and appropriate ongoing psychosocial support of the patient and the family is important. Genetic counselling should be provided to discuss X-linked inheritance. The discovery of the *SEDL*

gene has raised the possibility of carrier testing in females and prenatal testing for this condition.

Electronic database information and accession numbers

(OMIM was accessed at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM,); (XL-SEDT, MIM No. 313400); (*SEDL* gene, MIM No. 300202, GenBank No. AH008075).

Acknowledgements

We thank G Sutherland and M Shaw for a critical reading of the manuscript. This work was carried out with the support of the National Health and Medical Research Council of Australia.

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