

**X-Linked Spondyloepiphyseal Dysplasia Tarda (SEDТ)
 via TRAPPC2 Gene Sequencing (Test #819)**

Brief Description of Clinical Features: X-linked SEDТ (OMIM#313400) is characterized by disproportionately short stature with short trunk and arm span significantly greater than height. At birth, affected males are normal in length and have normal body proportions. Around age six to eight years, those affected males begin to exhibit retarded linear growth. Final adult height is typically 4'10" to 5'6". Progressive joint and back pain with osteoarthritis ensues; hip, knee, and shoulder joints are commonly involved but to a variable degree. Hip replacement is often required as early as age 40 years (Tiller & Hannig. *GeneReviews* 2011).

Genetics: X-linked SEDТ is inherited in an X-linked recessive manner. *TRAPPC2* (previously known as *SEDL*) is the only gene in which mutations are known to cause X-linked SEDТ. *TRAPPC2* encodes sedlin, an evolutionarily conserved and ubiquitously expressed protein whose function remains poorly understood. Based on function of the yeast homolog, sedlin may be involved with intracellular protein trafficking, as part of the TRAPP (transport protein particle) complex (Jang et al. *J Biol Chem.* 277:49863–49869, 2002). Other studies have demonstrated localization of sedlin to the nucleus, where it interacts with various transcription factors (Liu et al. *J Cell Biochem* 109:1129–1133, 2010). Small deletions causing frameshifts and splice site mutations in *TRAPPC2* were found in more than half of reported X-linked SEDТ cases (Savarirayan et al. *Eur J Hum Genet* 11:639–642, 2003). Missense and nonsense mutations were a relatively less common type of mutation (Gedeon et al. *Am J Hum Genet* 68:1386–1397, 2001). Large deletions involving single or multiple exons had also been documented in different studies (Gedeon et al. 2001; Shaw et al. *Clin Genet* 64:235–242, 2003; Fiedler et al. *Hum Mutat* 24:103, 2004), though cumulatively accounting for only a small portion of cases.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *TRAPPC2* gene plus ~50 bp of flanking non-coding DNA on each side. We will also sequence any single exon (Test #100, \$190) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000023.10 mRNA: NM_014563.5
 Protein: NP_055378.1 mRNA and Protein: CCDS 48082.1

Indications for Test: Candidates for this test are patients with clinical and radiographic features consistent with X-linked SEDТ, and family members of patients who have known *TRAPPC2* mutations.

Sensitivity of Test: Sequencing of *TRAPPC2* is predicted to detect disease mutations in more than 80% of males with a clinical diagnosis of X-linked SEDТ (Gedeon et al. 2001; Fiedler et al. 2004).
 Note: *TRAPPC2* gene deletions are suspected in males based on failed amplification of single or multiple exons. Those large deletions would not be detected in female carriers by sequence analysis.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page four of the Requisition Form.

Prices:	Sequencing of TRAPPC2 gene	\$ 440	
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x4	83898 \$100	Sequencing x4	83904 \$160
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 80

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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