

**ROR2 Gene Sequencing (Test #136)
 Robinow Syndrome, Autosomal Recessive
 Brachydactyly, Type B1**

Brief Description of Clinical Features: Robinow syndrome is characterized by dysmorphic facial features, short stature, genital hypoplasia, shortening of the forearms, and other skeletal abnormalities. All patients exhibit hypertelorism and a small upturned nose. The majority of patients also have frontal bossing, prominent eyes, downslanting palpebral fissures, long philtrum, downturned triangular mouth, micrognathia, and crowded teeth. Mesomelic shortness is another universal finding, and most patients have small hands with clinodactyly. Thumbs and great toes are sometimes broad. Vertebral anomalies distinguish recessive Robinow syndrome (OMIM #268310) resulting from *ROR2* mutations from the dominant form (see below). Patients with recessive Robinow syndrome often have thoracic hemivertebrae, rib anomalies, and scoliosis while patients with the dominant form do not (von Bokhoven et al. *Nature Genet* 25:423-426, 2000). Brachydactyly occurs as part of many syndromes or as an isolated finding. *ROR2*-associated type B brachydactyly (OMIM #113000) can be distinguished from other nonsyndromic forms by shortening and hypoplasia of the distal phalanges, dysplasia or aplasia of the nails, and hypoplasia of the middle phalanges (Schwabe et al. *Am J Hum Genet* 67:822-831, 2000). Other distinguishing features are biphalangal digits, syndactyly, and bilateral symmetry of the abnormalities (Oldridge et al. *Nature Genet* 24:275-278, 2000).

Genetics: Both autosomal recessive and dominant forms of Robinow syndrome are known. Recessive Robinow syndrome is associated with loss of function mutations in *ROR2* (Ali et al. *Nature Genet* 25:419-422, 2000), many of which result in defective intracellular trafficking (Ali et al. *Hum Genet* 122:389-395, 2007). The *ROR2* gene (OMIM #602337) encodes a cell surface receptor tyrosine kinase involved in development of the skeletal, cardiovascular and genital systems. The etiology of dominant Robinow syndrome, which is clinically milder and probably the rarer form, is unknown. Type B1 brachydactyly is inherited as an autosomal dominant condition. Mutations that lead to truncation of the intracellular part of the protein after the tyrosine kinase domain cause dominant brachydactyly via a gain of function mechanism (Oldridge et al. 2000; Schwabe et al. 2000).

Description of This Particular Test: The receptor tyrosine kinase-like orphan receptor-2 protein is coded by exons 1-9 of the *ROR2* gene located on chromosome 9q22. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: **Genomic: NC_000009.10** **mRNA and Protein: CCDS 6691.1**

Indication for Testing: Individuals with clinical findings consistent with Robinow syndrome and recessive inheritance, or nonsyndromic brachydactyly with dominant inheritance.

Sensitivity of test: Clinical sensitivity should be high for Robinow syndrome when patients meet strict phenotypic criteria and evidence exists for recessive inheritance. Analytic sensitivity may be limited due to the presence of intragenic deletions (Brunetti-Pierri et al. *Am J Med Genet* 146A:2804-2809, 2008). Clinical and analytical sensitivity for type B1 brachydactyly should be high in cases with characteristic findings of the phalanges.

Turn Around Time: Maximum of 40 days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of ROR2 Gene	\$ 740		
CPT Codes:				
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40	
Amplification x 13	83898 \$ 210	Sequencing x13	83904 \$ 310	
Separation x1	83894 \$ 70	Interpretation/Report x1	83912 \$ 80	

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

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com