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Genetic Testing for Robinow Syndrome and Brachydactyly, type B1

Clinical Features:

- Patients with Robinow syndrome (RS) [OMIM #268310] have characteristic facial features, growth retardation, limb defects, and genital hypoplasia. Skeletal anomalies include mesomelic or acromesomelic limb shortening, hemivertebrae, and brachydactyly. Characteristic facial features include macrocephaly, prominent broad forehead, hypertelorism, midface hypoplasia, short upturned nose with depressed nasal bridge and flared nostrils, large triangular mouth, micrognathia, and low-set ears. Approximately 10-15% of individuals have developmental delay. Other features include heart defects (~15%), renal tract anomalies, rib fusions and nail hypoplasia or dystrophy. Approximately 10% of children with RS have an early fatal outcome due most likely to congenital heart defects. Patients with autosomal recessive RS (RRS) appear to be more severely affected than those believed to have autosomal dominant RS (DRS). Vertbral anomalies, radial head dislocations and scoliosis are rarely seen in DRS. Height is usually nearer the normal range in DRS (1, 2).
- Patients with brachydactyly, type B1 (BDB1) [OMIM #113000] have hypoplasia/aplasia of the distal phalanges and nails. Middle phalanges are short and terminal phalanges are rudimentary or absent. Usually, the thumbs and big toes are spared, but may have broadening or partial duplication. BDB1 is the most severe form of brachydactyly.

Molecular Genetics:

- Autosomal recessive Robinow syndrome—Mutations in the *ROR2* [OMIM #602337] gene have been identified in patients with RRS (3, 4). Afzal AR, *et al* [2000] reported that 10/10 consanguineous families with RRS had homozygous mutations in *ROR2* (4). Bokhoven H, et al [2000] found that 7/11 consanguineous families with RRS had homozygous mutations in *ROR2* (3). Approximately 65-100% of individuals with RRS have mutations in *ROR2.* Missense, nonsense, and frameshift mutations have been reported in both the intracellular and extracellular domains of the ROR2 protein. These mutations are predicted to be "loss-of-function" mutations and heterozygous carriers do not typically have a clinical phenotype (5).
- Autosomal dominant Robinow syndrome - To date, two missense mutations in *WNT5A* [OMIM#164975] have been identified in patients with DRS (6). Functional expression assays in zebrafish embryos showed that the mutant proteins represented hypomorphic alleles rather than dominant-negative mutations. Autosomal dominant Robinow syndrome is rarer than autosomal recessive Robinow syndrome.
- Brachydactyly, type B1—Heterozygous mutations of the *ROR2* [OMIM #602337] gene have been identified in patients with BDB1 (7). All of the *ROR2* mutations reported in patients with BDB1 have been truncating mutations in the intracellular domain of the protein. These mutations are predicted to be "gain-of-function" mutations. Those mutations distal to the tyrosine kinase domain cause a severe, amputation-like phenotype affecting three or more fingers, whereas proximal mutations produce a less severe phenotype (5).

ROR2 has 9 coding exons. The ROR2 protein is a member of the ROR kinase family with tyrosine kinase activity. It is highly expressed in the developing nervous system, chondrocytes, branchial arches, heart and limb buds during mouse development (3). *WNT5A* has 5 coding exons. *ROR2* is a putative *WNT5A* receptor and the WNT5A/ROR2 signal transduction pathway it important in human craniofacial and skeletal development (6).

Inheritance:

- Autosomal recessive Robinow syndrome—*ROR2* mutations that cause RRS are inherited in an autosomal recessive pattern. RRS is rare. It occurs more commonly in consanguineous families and those of Turkish and Omani origin. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

- Autosomal Dominant Robinow syndrome - *WNT5A* mutations that cause DRS are inherited in an autosomal dominant pattern. Recurrence risk for unaffected parents of an isolated case is <1%. Recurrence risk for affected individuals is 50%.
- Brachydactyly, type B1is inherited in an autosomal dominant pattern. Recurrence risk for affected individuals is 50%.

Additional Resources:

Robinow Syndrome Foundation
Phone: 763-434-1152
Karla Kruger email: robinowfoundation@comcast.net
www.robinow.org

Test methods:

We offer mutation analysis of all coding exons and intron/exon boundaries of *ROR2* and *WNT5A* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *ROR2* and *WNT5A* genes by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Please send a completed RRS/BDB1 Clinical Checklist and patient consent form with each sample.

ROR2 sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81405
Turn-around time:	4 - 6 weeks

ROR2 deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
Turn-around time:	4 weeks

WNT5A sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
Turn-around time:	4 - 6 weeks

WNT5A deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Bacino C. ROR2-Related Robinow Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2005.
2. Mazzeu JF, Pardono E, Vianna-Morgante AM et al. Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome. Am J Med Genet A 2007: 143: 320-325.
3. van Bokhoven H, Celli J, Kayserili H et al. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome. Nat Genet 2000: 25: 423-426.
4. Afzal AR, Rajab A, Fenske CD et al. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. Nat Genet 2000: 25: 419-422.
5. Afzal AR, Jeffery S. One gene, two phenotypes: ROR2 mutations in autosomal recessive Robinow syndrome and autosomal dominant brachydactyly type B. Hum Mutat 2003: 22: 1-11.
6. Person AD, Beiraghi S, Sieben CM et al. WNT5A mutations in patients with autosomal dominant Robinow syndrome. Dev Dyn 2010: 239: 327-337.
7. Oldridge M, Fortuna AM, Maringa M et al. Dominant mutations in ROR2, encoding an orphan receptor tyrosine kinase, cause brachydactyly type B. Nat Genet 2000: 24: 275-278.

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