THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Rhizomelic Chondrodysplasia Punctata

Clinical Features:

Rhizomelic Chondrodysplasia Punctata (RCDP) is a peroxisomal disorder characterized by disproportionately short stature primarily affecting the proximal parts of the extremities, congenital contractures, characteristic ocular involvement, severe intellectual disability and spasticity. Characteristic facial features include broad nasal bridge, epicanthus, high-arched palate, dysplastic external ears and micrognathia. RCDP presents in the neonatal period and most affected individuals die in the first decade of life, although milder forms of RCDP can present with variable growth and developmental delays and survival into adulthood (1).

Molecular and Biochemical Genetics:

Mutations in *PEX7* [OMIM#601757] account for more than 90% of patients with RCDP1 [OMIM#215100] (2). The finding of a deficiency of plasmalogens in red blood cells, increased plasma concentration of phytanic acid, and normal plasma concentration of very long chain fatty acids is consistently identified in individuals with PEX7 mutations (1). *PEX7* is one of sixteen *PEX* genes that are involved in mammalian peroxisome assembly. Mutations in *GNPAT* [OMIM#222765] and *AGPS* [MIM#600121] account of less than 10% of patients with RCDP2 [OMIM#222765] and RCDP3 [OMIM#60012] respectively (2). PEX7 transports AGPS into the peroxisome, where AGPS and GNPAT partner on the luminal membrane surface.

Inheritance:

RCDP follows an autosomal recessive inheritance pattern. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%. The prevalence of RCDP1 is estimated to be less than 1 in 100,000.

Test methods:

Our RCDP panel includes full gene sequencing for the *PEX7, GNPAT* and *AGPS* genes. Testing includes sequence analysis of all 10 coding exons and intron/exon boundaries of *PEX7*, all 16 coding exons and intron/exon boundaries of *GNPAT,* and all 20 coding exons and intron/exon boundaries of *AGPS* by direct sequencing of amplification products in both the forward and reverse directions.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.
This information will be used to aid in interpretation of the test result. The clinical data form, along with the test result, will be shared with Dr. Dobyns and stored anonymously in a *GPR56* database. Patients with BFPP, with or without *GPR56* gene mutations, can enroll in Dr. Dobyns' research study.

Rhizomelic Chondrodysplasia Punctata Panel (*PEX7, GNPAT,* and *AGPS*)

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
	81407
Turn-around time:	4 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.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Braverman NE, D'Agostino MD, Maclean GE. Peroxisome biogenesis disorders: Biological, clinical and pathophysiological perspectives. Dev Disabil Res Rev 2013: 17: 187-196.
2. Itzkovitz B, Jiralerspong S, Nimmo G et al. Functional characterization of novel mutations in GNPAT and AGPS, causing rhizomelic chondrodysplasia punctata (RCDP) types 2 and 3. Hum Mutat 2012: 33: 189-197.

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