PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Arthrogryposis-Renal Dysfunction-Cholestasis (ARC) Syndrome *via VIPAR* Gene Sequencing (Test #591)

Brief Description of Clinical Features: Arthrogryposis, renal dysfunction, and cholestasis syndrome (ARC syndrome; OMIM #208085) is a multisystem disorder with features of arthrogryposis multiplex congenita, renal tubular hypoplasia, and cholestatic liver disease (Di Rocco et al. *Am J Med Genet* 37:237-240, 1990; Di Rocco et al. *Eur J Pediatr* 154:835-839, 1995). Life-threatening complications of malabsorption secondary to cholestatic jaundice appear shortly after birth (Nezelof et al. *J Pediatrics* 94:258-260, 1979). The majority of patients succumb in several weeks to several months of life (Gissen et al. *Hum Genet* 120:396-409, 2006). Renal disease involves renal tubular cell degeneration and nephrocalcinosis (Saraiva et al. *Clin Lab Obs* 117:761-763, 1990). Liver histology in ARC syndrome has been reviewed (Horslen et el. *J Med Genet* 31:62-64, 1994). Bile duct hypoplasia and low gamma glutamyl transpeptidase activity are documented (Gissen et al. 2006). Other clinical findings described in a cohort of 62 ARC syndrome patients include failure to thrive (100%) and structural cardiac defects (10%) (Gissen et al. 2006). The same study found a high rate of life-threatening hemorrhagic events during diagnostic organ biopsy procedures. Severe osteopenia with congenital fractures has been reported in one ARC syndrome patient (Taha et al. *Am J Med Genet* 143A:2835-2837, 2007).

Genetics: ARC syndrome is inherited as an autosomal recessive disorder. *VPS33B* was found to be a causative gene for ARC syndrome (Gissen et al. *Nat Genet* 36:400-404, 2004), and is thought to account for approximately 75% of cases (Cullinane et al. *Nature Genet* 42:303-312, 2010). Mutations in the *VIPAR* gene, which encodes a 'VPS33B-interacting protein', have been found in all cases of classic ARC syndrome when *VPS33B* mutations were not identified (Cullinane et al. 2010). All reported *VIPAR* mutations result in premature protein termination.

Description of This Particular Test: The *VIPAR* gene, also known as *C14orf133*, encodes a protein that interacts with the *VPS33B* gene product to regulate membrane fusion. The *VIPAR* gene is located on chr 14q24 and consists of 19 coding exons. Testing is accomplished by amplifying each coding exon (exons 3-21) 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_000014.8** **mRNA: NM_022067.2**
Protein: NP_071350.2 **mRNA and Protein: CCDS 9862.1**

Indication for Testing: Individuals with the triad of symptoms of arthrogryposis multiplex congenita, renal dysfunction, and cholestasis and who have negative test results for the *VPS33B* gene.

Sensitivity of test: Analytical sensitivity should be high because all mutations reported to date are detectable by direct sequence analysis of genomic DNA. Clinical sensitivity appears to be high in patients with classic symptoms and who test negative for *VPS33B* mutations.

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

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *VIPAR*, exons 3-21** **$ 1020**

CPT Codes:

Sample Ascertainment	83890	$ 30	DNA Isolation	83891	$ 40
Amplification x19	83898	$ 300	Sequencing x19	83904	$ 440
Separation	83894	$ 90	Interpretation/Report	83912	$ 120

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

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