PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Arthrogryposis-Renal Dysfunction-Cholestasis (ARC) Syndrome *via VPS33B* Gene Sequencing (Test #248)

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. *J Pediatrics* 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* (OMIM #608552) 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. 2010). Nonsense and splice site mutations represent the most common forms of *VPS33B* mutation although missense and frame-shifting mutations are also reported. 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. *Nature Genet* 42:303-312, 2010).

Description of This Particular Test: The *VPS33B* gene encodes a homolog of the yeast vacuolar sorting protein *Vps33.* The *VPS33B* gene is located on chr 15p26.1, and its product is a cytosolic protein involved in vesicle membrane fusion. Testing is accomplished by amplifying each coding exon (exons 1 – 23) 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_000015.9** **mRNA: NM_018668.3**
Protein: NP_061138.3 **mRNA and Protein: CCDS 10369.1**

Indication for Testing: Individuals with the triad of symptoms of arthrogryposis multiplex congenita, renal dysfunction, and cholestasis.

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 also. Twenty-eight of 35 ARC syndrome families in one study were found to have two *VPS33B* mutations (Gissen et al. 2006).

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 *VPS33B*, exons 1-23** **$ 1090**

CPT Codes:

Sample Ascertainment	83890	$ 30	DNA Isolation	83891	$ 40
Amplification x22	83898	$ 330	Sequencing x22	83904	$ 500
Separation	83894	$ 70	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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