

Palmoplantar Keratoderma with Arrhythmogenic Right Ventricular Cardiomyopathy and Woolly Hair/Naxos Disease via *JUP* Gene Sequencing -- Test #208

Brief Description of Clinical Features: Palmoplantar Keratoderma with Arrhythmogenic Right Ventricular Cardiomyopathy and Woolly Hair, also known as Naxos disease (OMIM 601214) is a cardiocutaneous syndrome characterized by non-epidermolytic palmoplantar keratosis, woolly hair, and the typical cardiac features of arrhythmogenic right ventricular dysplasia. Usual symptoms include diffuse palmar and plantar keratosis, dense dull, bristly scalp hair, recurrent tachycardia, and palpitation. Additional symptoms include short fingers, curved nails, small hands and arms, atrial fibrillation, collapse and syncope. Naxos disease was first reported in patients from the Greek island Naxos (Protonotarios et al. Br Heart J 56:321-326, 1986). The cutaneous symptoms begin in early infancy, while the cardiac symptoms are manifested during puberty, often with syncope. Sudden death occurs in approximately 2% of patients (Protonotarios J Am Coll Cardiol 38:1477-1484, 2001). Naxos disease affects ~ 1/1000 people in the Greek islands (Protonotarios and Tsatsopoulou Cardiovasc Pathol 13:185-194, 2004).

Genetics: Naxos disease is inherited in an autosomal recessive manner. In patients of Greek origin, Naxos disease is caused by a homozygous 2 bp-deletion in the *JUP* gene. This deletion is defined as c.2157delTG, and causes a frameshift leading to premature protein termination (McKoy et al. Lancet 355:2119-2124, 2000). Over 90% of homozygous individuals for the c.2157delTG have electrocardiographic abnormalities; while only minor ECG changes were detected in 25% of heterozygous carriers, who are clinically unaffected (Protonotarios J Am Coll Cardiol 38:1477-1484, 2001). The 2 bp-deletion was also reported in Naxos patients of Turkish origin. Naxos disease is genetically heterogeneous, as suggested by the absence of *JUP* mutations in Arab families (Djabali et al. J Invest Dermatol 118:557-560, 2002). In addition to Naxos disease, a heterozygous *JUP* 3bp-insertion (c.116_118dupGCA) was reported in a German family with arrhythmogenic right ventricular cardiomyopathy but no cutaneous abnormality (Asimaki et al. Am J Hum Genet 81:964-973, 2007). The *JUP* gene encodes junction plakoglobin, which is an important element of cell-cell adhesion complexes.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons (exons 2-14) of the *JUP* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As requested, we will also sequence only exon 12 (Test #100) which harbors the c.2157delTG mutation.

Reference Sequences: Genomic: NC_000017.10 mRNA: NM_021991.2 Protein: NP_068831.1 (CCDS 11407.1)

Indications for Test: Patients with clinical features consistent with Naxos disease are candidates. Naxos patients of Greek or Turkish origin are candidates for sequencing exon 12. Patients with ARVC and no mutations in the most common ARVC genes are also candidates for this test.

Sensitivity of Test: Sequencing of exon 12 is expected to detect mutations in all Naxos patients of Greek origin (McKoy et al. 2000).

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

Specimen Requirements: See page 4 of the Requisition Form.

Prices:	Sequencing of the full <i>JUP</i> gene \$ 730	Sequencing of Exon 12 only (Test #100) \$190
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x11	83898 \$200	Sequencing x11 83904 \$ 310
Separation x1	83894 \$ 60	Interpretation/Report x1 83912 \$ 90

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

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