Cincinnati Children's
Heart Institute

Heart Institute Diagnostic Lab

CAP#: 7518730

CLIA#: 36D2003208

Phone: (513) 803-1751

Fax: (513) 803-1748

Email: HeartDx@cchmc.org

CAV3 Sequencing

The *CAV3* gene encodes caveolin-3, a protein which forms caveolae and is expressed in cardiomyocytes and skeletal muscle (1). Caveolae are flask-shaped invaginations of the plasma membrane and function in membrane integrity, vesicular trafficking, and signal transduction (2). Traditionally, mutations in *CAV3* genes have been linked to a group of muscle diseases, Caveolinopathies, with four distinct phenotypes: limb girdle muscular dystrophy-1C, rippling muscle disease, hyperCKemia, and distal myopathy (2). However, recent studies have shown mutations in *CAV3* to cause cardiac disease in the absence of skeletal muscle findings. Cardiac ion channels have been localized to caveolae in cardiomyocytes, and although the exact mechanism has not been identified, *CAV3* mutations have been shown to modify the kinetics of closely associated ion channels (1, 2). A loss of caveolin-3 in mice has been shown to cause hyperactivation of the p42/44 mitogen-activated protein kinase cascade that plays a role in cardiac hypertrophy (5, 6). Mutations have been identified in individuals with Long-QT Syndrome, Sudden Infant Death Syndrome, and Familial Hypertrophic Cardiomyopathy (1, 3, 4, 5).

The *CAV3* gene is mapped to chromosome 3p25 and contains two coding exons. The mutations in *CAV3* that have caused traditional Caveolinopathies have been inherited in an autosomal dominant manner although rare autosomal recessive mutations have been described. The majority of these mutations are missense (2).

Indication

Molecular confirmation of a suspected Caveolinopathy. In the absence of skeletal muscle disease, can be considered in cases of LQTS, Sudden Infant Death Syndrome, or Hypertrophic Cardiomyopathy.

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center

Attn: Heart Institute Diagnostic Lab

240 Albert Sabin Way,
Room S4.381

Cincinnati, OH 45229-3039

Methodology:

Both coding exons as well as the exon/intron boundaries and a portion of untranslated regions of the gene(s) are amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an *ABI PRISM® 3730 DNA Analyzer*. Sequence variants different from National Center for Biotechnology Information GenBank references are further evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exons 1 and 2 of *CAV3* are detectable by sequence based methods.

References:

1. Vatta, M., Ackerman, M.J., Ye, B., et al. (2006). Mutant Caveolin-3 Induces Persistent Late Sodium Current and Is Associated with Long-QT Syndrome. *Circulation*. 114:2104-2112.
2. Gazzero, E., Sotgia, F., Bruno, C., et al. (2010). Caveolinopathies: from the biology of caveolin-3 to human diseases. *European Journal of Human Genetics*. 18: 137-145.
3. Arnestad, M., Crotti, L., Rognum, T.O., et al. (2007). Prevalence of Long-QT Syndrome Gene Variants in Sudden Infant Death Syndrome. *Circulation*. 115: 361-367.
4. Cronk, L.B., Ye, B., Tester, D.J., et al. (2006). Identification of CAV3-encoded caveolin-3 mutations in sudden infant death syndrome. *Heart Rhythm*. 3(Suppl): S66.
5. Hayashi, T., Arimura, T., Ueda, K., et al. (2003). Identification and functional analysis of a caveolin-3 mutation associated with familial hypertrophic cardiomyopathy. *Biochemical and Biophysical Research Communiations*. 313: 178-184.
6. Woodman, S.E., Park, D.S., Cohen, A.W., et al. (2002). Caveolin-3 knock-out mice develop a progressive cardiomyopathy and show hyperactivation of the p42/44 MAPK cascade. *The Journal of biological chemistry*. 277 (41): 38988-38997.

Specimen:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation Analysis 2-4 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Genome Sequencing	81404
Additional Family Members	81403