

Heart Institute Diagnostic Lab

CAP#: 7518730

CLIA#: 36D2003208

Phone: (513) 803-1751

Fax: (513) 803-1748

Email: HeartDx@cchmc.org

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

KCNJ2 – Andersen-Tawil Syndrome, Long QT Syndrome

Andersen-Tawil syndrome (ATS) is a hereditary disorder characterized by periodic paralysis, Long QT intervals (with ventricular arrhythmias), and dysmorphic features including low set ears, ocular hypertelorism, small mandible, fifth digit clinodactyly, syndactyly, and scoliosis. The prevalence is unknown, but estimated to affect 1/100,000 individuals. ATS is caused by mutations in the *KCNJ2* gene, which codes for a potassium channel (Kir2.1) present in both cardiac and skeletal muscle. Most mutations in *KCNJ2* lead to a dominant-negative suppression of the Kir2.1 channel function, which affects both resting membrane potential and modulation of excitation^{1,2}. The *KCNJ2* gene contains 2 exons and is located on chromosome 17q23.1-q24.2.

KCNJ2 is the only gene known to cause ATS and causative mutations can be identified in approximately 70% of individuals who meet the diagnostic criteria². Most of these mutations are located within exon 2 of the gene. Since causative mutations can not be identified in all affected individuals, it is likely that other unidentified genes also contribute to the development of ATS. Approximately 50% of *KCNJ2* mutations are parentally inherited, and the remaining 50% are de novo. The inheritance pattern for ATS is autosomal dominant, with variable penetrance. Approximately 80% of individuals manifest symptoms¹. It is important to note that there are other known causes of periodic paralysis in the absence of the other clinical features of ATS.

Indication

KCNJ2 gene testing is utilized to confirm a diagnosis of ATS in patients with clinically evident disease. Genetic testing also allows for early identification and diagnosis of individuals at greatest risk prior to the expression of typical clinical manifestations and can be used for prenatal diagnosis. If a mutation is identified in an asymptomatic individual, regular and routine outpatient follow up is indicated. If clinically unaffected members of a family with an identified mutation for ATS are found not to carry that mutation, they can be definitely diagnosed as unaffected and reassured that neither they nor their children will be at higher risk compared to the general population to develop symptoms related to ATS. A negative test result in an individual with a known familial mutation also eliminates the need for routine follow up.

Methodology:

Exon 2, the only coding exon of the *KCNJ2* gene, as well as the exon/intron boundary and portion of untranslated regions of the gene 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 1-2 of *KCNJ2* are detectable by sequence based methods. Sequencing does not detect deletions or duplications.

References:

1. Tristani-Firouzi M, Jensen JL, Donaldson MR, Sansone V, Meola G, Hahn A, Bendahhou S, Kwiecinski H, Fidzianska A, Plaster N, Fu YH, Ptacek LJ, Tawil R. Functional and clinical characterization of *KCNJ2* mutations associated with LQT7 (Andersen syndrome). *The Journal of Clinical Investigation*. 2002;110:381-388.
2. Lange PS, Er F, Gassanov N, Hoppe UC. Andersen mutations of *KCNJ2* suppress the native inward rectifier current IK1 in a dominant-negative fashion. *Cardiovascular Research*. 2003;59:321-327.

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 Gene Sequencing 81479

Additional Family Members 81403