



# The One

*a publication that highlights new tests and announcements from ARUP*

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\* Please note that test details contained in this publication may change. For the most up-to-date test information, please review ARUP's technical bulletins at <http://www.aruplab.com/Testing-Information/technicalbulletins.jsp>.

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## Upcoming Trade Shows

### JUNE 15-17

G-2 Laboratory Outreach; Las Vegas, NV

### JUNE 27-28

Healthcare Financial Management Association (HFMA); Orlando, FL

### JULY 26-28

American Association for Clinical Chemistry (AACC); Atlanta, GA

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# ARUP Announces Changes to the Standard Transport Tube

Available May 2011

## Maximum Capacity

The printing has changed on all ARUP standard transport tubes. This change was implemented to help clients view the new maximum specimen capacity allowed for submission. The new tubes have graduated markings up to 4 mL, which is now the maximum specimen capacity. The additional air space at the top of the tube is critical in allowing for expansion and preventing leakage. For this reason, liquid should never exceed 4 mL. If

specimen requirements indicate more than 4 mL, the specimen should be submitted in multiple tubes.

## Label Position

Follow the printed instructions on the tube. The top edge of the label should line up next to the graduated markings and be at least ¼ inch from the bottom of the tube.

# Chromogranin A (0080469) Test Kit Change

Effective May 16, 2011, ARUP Laboratories will change the test kit for the assay Chromogranin A (test code 0080469) to enhance reliability. Due to differences in the analytical components of the current and replacement kits, test results obtained with each cannot be used interchangeably.

To facilitate a comparison and rebaselining of individual patient results, specimens received for chromogranin A testing will be

analyzed with both the current and replacement tests beginning on March 16, 2011, and the results of both tests will be reported. Chromogranin A concentrations as determined by the current assay will be reported until May 15, 2011, or until the supply of current kits is exhausted.

Questions and concerns may be directed to ARUP Client Services at (800) 522-2787.

# Immunohistochemistry Stain and Return Service

To better serve clients who use the ARUP Immunohistochemistry Stain and Return Service, a new test-request form, which lists the most common immunohistochemistry stains performed, was created. Each stain will now have its own test code number, allowing clients to order stains electronically. Stains not listed on the form can be found in the ARUP Laboratory Test Directory.

This form can be used for all Immunohistochemistry Laboratory stain requests, including those that are performed by the

laboratory staff and then analyzed by an ARUP pathologist (e.g., MSI, HercepTest™, ER/PR, etc.). Surgical and hematopathology consults remain available only through the Anatomic Pathology Test Request Form (#32960). The Immunohistochemistry Stain Offering Form can be ordered by contacting ARUP Client Services at (800) 522-2787 and requesting reorder #32978.

# Angelman Syndrome: Methylation

DNA testing to confirm a clinical suspicion/diagnosis of Angelman Syndrome

## Disease Overview

- Angelman syndrome (AS) is characterized by severe developmental delay or mental retardation, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and unique behaviors with an inappropriately happy demeanor.
- At birth, newborns with AS have normal head circumference and no major birth defects.
- Infants with AS can present with feeding problems and generalized oral-motor incoordination followed by developmental delays at 6–12 months of age.
- Children with AS develop microcephaly by age 2; seizures and characteristic EEG pattern by age 3.
- Speech impairment is severe, with little to no development of expressive language.
- Most children with AS learn to walk between 30 months and 6 years of age, but 10 percent remain non-ambulatory.
- Unique behaviors may include frequent laughter, happy demeanor, excitability, hand flapping, short attention span, sleep disturbances, and abnormal food-related behaviors.
- Individuals may have dysmorphic features such as flat occiput, occipital groove, wide mouth and protruding tongue, prognathism, and strabismus. Hypopigmented skin, as well as light hair and eye color relative to the family members, may be present.
- Affected adults require assistance living arrangements. Both men and women have normal fertility and near-normal life span.
- There is currently no effective treatment of AS. Management includes antiepileptic drugs to control seizures; orthotic braces or surgery for scoliosis and other orthopedic problems; safe night-time confinement; physical, speech, and occupational therapy; behavioral modifications; individual educational plans; and weight control.

## Epidemiology

- Prevalence is approximately 1:15,000, with males and females equally affected.

## Genetics

- Angelman syndrome is caused by lack of functional maternal copy of the *UBE3A* gene on chromosome 15q11.2-q13.
- Ubiquitin protein ligase (*UBE3A*), or E6-associated protein (E6-AP), is an E3 ligase that functions in the E3 complex of the ubiquitin cycle.
- *UBE3A*, which is expressed only from the maternal allele in fetal and adult brain prefrontal cortex neurons, may be regulated through paternally expressed antisense transcript. The *UBE3A* protein controls synaptic function by ubiquitinating and degrading the synaptic protein arc.

- Disruption of degradation of a number of *UBE3A* substrates is thought to be responsible for the phenotypic effects of AS.
- The etiology of AS is as follows:
  - Maternal deletion involving 15q11.2-q13 (68 percent).
  - Paternal uniparental disomy for chromosome 15 (7 percent).
  - *UBE3A* mutation (11 percent).
  - Imprinting center defect (3 percent).
  - Cytogenetically visible chromosomal translocation (< 1 percent).
  - Presently unidentified genetic mechanism (10 percent).
- Determining the molecular mechanism responsible for AS is important for accurate genetic counseling regarding recurrence risk.
- Inheritance varies depending upon the molecular genetic mechanism. *UBE3A* mutations identified by sequencing may be maternally inherited or de novo.
- Offspring of a female carrier of a *UBE3A* sequence mutation are at 50 percent risk for AS.
- A few individuals with AS have been found to have complete or partial *UBE3A* gene deletions.
- Mosaicism for germline *UBE3A* mutations has been reported. As molecular testing cannot exclude maternal germline mosaicism, prenatal testing for the familial *UBE3A* mutation should be offered in subsequent pregnancies to all females who have a child with AS.

## Indications for Ordering

- To establish a diagnosis of AS in individuals with clinical symptoms. DNA methylation analysis identifies approximately 78 percent of individuals with AS and is the most sensitive diagnostic test.

## Interpretation

- Unaffected individuals have a methylated, maternally inherited and an unmethylated, paternally inherited allele detectable by methylation-specific PCR. Absence of the methylated maternal allele is indicative of AS.
- An abnormal methylation result should be followed by FISH or array CGH to determine if a deletion is present. If a deletion is present, chromosome analysis should be performed to exclude a chromosome rearrangement that may alter recurrence risk.
- If FISH analysis is normal, DNA polymorphism analysis should be performed to distinguish between paternal UPD and an imprinting defect.
- If there is no UPD, further DNA studies can determine if an imprinting center deletion is present.
- Parental testing may be indicated to determine if chromosomal deletions, chromosomal rearrangements, or gene mutations are de novo.

## Angelman Syndrome: Methylation, continued

### Methodology and Limitations

- Bisulfate conversion and PCR amplification to detect methylation using melting-curve analysis.
- Other molecular mechanisms resulting in AS will not be assessed.

### Related Tests

- Chromosome FISH, Metaphase (Angelman Syndrome) (2002299)
- Rett Syndrome (*MECP2*), Sequencing & Deletion/Duplication (0051614)

### References

1. Chamberlain SJ, Lalande M. Angelman syndrome, a genomic imprinting disorder of the brain. *J Neurosci* 2010;30:9958–63.
2. GeneTests. <http://www.genetests.org> (accessed on April 4, 2011).
3. Greer PL, et al. The Angelman syndrome protein Ube3A regulates synapse development by ubiquitinating arc. *Cell* 2010;140:704–16.
4. Lossie AC, et al. Distinct phenotype distinguish the molecular classes of Angelman syndrome. *J Med Genet* 2001;38:834–45.
5. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. *Genet Med* 2010;12:385–95.

For specific collection, transport, and testing information, refer to Angelman Syndrome and Prader-Willi Syndrome by Methylation (2005077) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# BCR-ABL1, Major (p210) Quantitative

Quantitative detection of *BCR-ABL1* RNA with the major breakpoint (p210)

## Clinical Background

- Cases of chronic myelogenous leukemia (CML) and a subset of cases of acute lymphoblastic leukemia (ALL) harbor the t(9;22)(q34;q11) breakpoint, resulting in the *BCR-ABL1* p210 fusion oncogene (Philadelphia chromosome).
- For CML patients, the introduction of tyrosine kinase inhibitor therapy has greatly improved clinical outcome.<sup>1,2</sup> Quantitative PCR (qPCR)-based monitoring is critical for the assessment of important treatment milestones, such as major molecular response (MMR), and is also helpful for the early detection of emerging drug resistance.<sup>3,4</sup>
- A standardized reporting scale (international scale; IS) for *BCR-ABL1* p210 mRNA levels has been developed, enabling the comparison of serial data sets regardless of laboratory of origin or specific qPCR test methodology.<sup>5</sup>
- Nearly all CML patients and a subset of Philadelphia chromosome-positive ALL patients exhibit the p210 *BCR-ABL1* fusion resulting from a translocation between *BCR* exons 13 or 14 and *ABL1* exon 2 (e13a2, e14a2). This test is specific for *BCR-ABL1* mRNA with the major breakpoint resulting in the p210 form.

## Indications for Ordering

- The principal use for this test is to monitor the levels of *BCR-ABL1* fusion mRNA in whole blood from CML and ALL patients with confirmed major breakpoint Ph+ leukemia.

## Interpretation

- Results of this test are reported as follows:
  - Positive (percent on international scale)
  - Weakly positive, non-quantifiable
  - Not detected

## Limitations

- Results of this test must always be interpreted in the context of morphologic and other relevant data, and should not be used alone for a diagnosis of malignancy.
- Samples that are negative by this test may still harbor *BCR-ABL1* positive cells at levels below the limit of detection.
- This test does not detect *BCR-ABL1* mRNA with the minor breakpoint (e1a2; p190).

## Methodology

- Total RNA is extracted and converted to random-primed cDNA.
- A fragment spanning the *BCR-ABL1* major fusion breakpoint and a normalization control fragment within the *ABL1* cDNA are amplified by quantitative real-time PCR using the *BCR-ABL* Mbc Fusion Quant MMR Kit from Ipsogen.
- Standard curves are generated with every run, and the normalized copy number (NCN) of *BCR-ABL1/ABL1* is calculated.
- Each run includes IS-calibrated QC reagents, which allows patient data to be efficiently and accurately expressed on the IS.

## References

1. O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348(11):994-1004.
2. Jabbour E, et al. Choosing the best treatment strategy for chronic myeloid leukemia patients resistant to imatinib: weighing the efficacy and safety of individual drugs with *BCR-ABL* mutations and patient history. *Leukemia* 2010;24(1):6-12.
3. Hughes TP and Branford S. Monitoring disease response to tyrosine kinase inhibitor therapy in CML. *Hematology Am Soc Hematol Educ Program* 2009:477-87.
4. Press RD, et al. Determining the rise in *BCR-ABL* RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. *Blood* 2009;114(13):2598-605.
5. Müller MC, et al. Harmonization of molecular monitoring of CML therapy in Europe. *Leukemia* 2009;23(11):1957-63.

For specific collection, transport, and testing information, refer to *BCR-ABL1, Major (p210), Quantitative (2005017)* on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# BCR-ABL1, Minor (p190) Quantitative

Quantitative detection of *BCR-ABL1* mRNA with the minor breakpoint (p190)

## Clinical Background

- The t(9;22)(q34;q11) breakpoint resulting in the p190 *BCR-ABL1* fusion is found in a subset of cases of acute lymphoblastic leukemia<sup>1</sup> and rarely in cases of chronic myelogenous leukemia (CML).<sup>2</sup>
- Detection and monitoring of *BCR-ABL1* p190 fusions by quantitative PCR (qPCR) can be used for diagnosis, prognosis, and ongoing therapeutic monitoring.
- The p190 *BCR-ABL1* fusion results from a translocation between *BCR* exon 1 and *ABL1* exon 2 (e1a2). This test is specific for *BCR-ABL1* p190 fusions.

## Indications for Ordering

- The principal use for this test is monitoring the levels of *BCR-ABL1* fusion mRNA in whole blood from patients with confirmed minor-breakpoint Ph+ leukemia.

## Interpretation

- Results of this test are reported as follows:
  - Positive (normalized *BCR-ABL1* copy number)
  - Weakly positive, non-quantifiable
  - Not detected

## Limitations

- Results of this test must always be interpreted in the context of morphologic and other relevant data, and should not be used alone for a diagnosis of malignancy.
- Samples that are negative by this test may still harbor *BCR-ABL1* positive cells at levels below the limit of detection.
- This test does not detect *BCR-ABL1* mRNA with the major breakpoint (e13a2, e14a2; p210).

## Methodology

- Total RNA is extracted and converted to random-primed cDNA.
- A fragment spanning the *BCR-ABL1* minor fusion breakpoint and a normalization control fragment within the *ABL1* cDNA are amplified by quantitative real-time PCR using the *BCR-ABL1* e1a2 mbc/ABL Fusion Quant Kit from Ipsogen.
- Standard curves are generated with every run, and the normalized copy number (NCN) of *BCR-ABL1/ABL1* is calculated.

## References

1. Swerdlow SH, et al. 2008. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon, France: International Agency for Research, 439.
2. Verma D, et al. Chronic myeloid leukemia (CML) with p190 *BCR-ABL*: analysis of characteristics, outcomes and prognostic significance. *Blood* 2009;114(11):2232–5.

For specific collection, transport, and testing information, refer to *BCR-ABL1, Minor (p190), Quantitative (2005016)* on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# CDKL5-Related Disorders Sequencing and Deletion/Duplication

To confirm a diagnosis of X-linked infantile spasm syndrome or Atypical Rett Syndrome

## Disease Overview

- Germline mutations in the cyclin-dependent kinase-like 5 (*CDKL5/STK9*) gene are associated with early-onset intractable seizures and severe developmental delay, and result in a range of clinical phenotypes, including X-linked infantile spasm syndrome (ISSX) and atypical Rett syndrome.
- Individuals with germline mutations in either the *MECP2* or *CDKL5* genes may have overlapping clinical features, as both genes are involved in the same molecular pathway and exhibit similar expression patterns during development.
- Classic Rett syndrome is a severe, progressive neurodevelopmental disorder caused by germline mutations in the *MECP2* gene. Rett syndrome is characterized by rapid developmental regression and deceleration of head growth, as well as loss of speech, purposeful hand movements, and motor skills after 6 to 18 months of age.
- Atypical Rett syndrome includes the Hanefeld variant and X-linked infantile spasm syndrome (ISSX). ISSX, also known as West syndrome, is characterized by severe infantile spasms and mental retardation, lack of developmental progression, and hypsarrhythmia on EEG. The Hanefeld variant is used to describe females with early-onset epileptic seizures or infantile spasms with Rett-like features.
- Females with *CDKL5* mutations commonly present with infantile spasms or epileptic seizures within the first 6 months of life, a later intractable epileptic seizure disorder, mental retardation, hypotonia, and limited developmental progression.
- Males with *CDKL5* mutations may present with early-onset intractable epilepsy, severe encephalopathy, and profound mental retardation, although less severe phenotypes have been reported.

## Prevalence

- The incidence of disorders associated with *CDKL5* gene mutations is unknown.
- *CDKL5* mutations are more common in females than males.

## Genetics

- X-linked dominant inheritance; reported cases occur due to de novo mutations.
- At least 60 distinct pathogenic *CDKL5* mutations have been reported, the majority of which are sequence variants.
- Large deletions/duplications in the *CDKL5* gene have been reported in males and females. In one small series, three partial or complete *CDKL5* gene deletions/duplications represented half of identifiable mutations.
- Approximately 17 percent of females with early-onset epileptic seizures carry a *CDKL5* mutation.

- Genotype/phenotype correlations are not well established. Skewed X-inactivation patterns in females with *CDKL5* mutations may help explain phenotypic variability.

## Indications for Ordering

- To confirm a clinical diagnosis of a *CDKL5*-related disorder in individuals with infantile seizures, ISSX, *MECP2*-negative atypical Rett syndrome, autism, or mental retardation and seizure disorder.

## Contraindications

- Testing for individuals with a previously identified familial *CDKL5* mutation. To test individuals for a specific *CDKL5* sequence variant, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test code 2001961) and provide a copy of the lab report detailing the familial mutation.
- Prenatal testing.

## Interpretation

- Identification of a known pathogenic *CDKL5* mutation in a symptomatic individual predicts the presence of a *CDKL5*-related disorder. Clinical phenotypes may vary.
- Lack of an identifiable *CDKL5* mutation in a clinically affected individual decreases, but does not exclude, a diagnosis of a *CDKL5*-related disorder. Medical management should rely on clinical findings and family history.
- *CDKL5* sequence variants of unknown clinical significance may be detected by sequencing.

## Methodology

- PCR and bidirectional sequencing of the *CDKL5* coding region and intron-exon boundaries.
- Multiplex ligation-dependent probe amplification (MLPA) of the *CDKL5* gene includes all coding exons except exon 3.
- The combined clinical sensitivity of *CDKL5* sequencing and deletion/duplication testing is dependant on phenotype; 17 percent of females with early-onset epileptic encephalopathy have *CDKL5* mutations.
- Analytical sensitivity and specificity of sequencing and MLPA are 99 percent.

## Limitations

- Deep intronic mutations and some regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large deletions/duplications detected in *CDKL5* will not be determined.

## CDKL5-Related Disorders Sequencing and Deletion/Duplication, continued

### Related Tests

- CDKL5-Related Disorders (CDKL5) Sequencing (2004931)
- CDKL5-Related Disorders (CDKL5) Deletion/Duplication (2004927)
- Familial Mutation, Targeted Sequencing (2001961)

### References

1. Archer HL, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet* 2006;43:729–34.
2. Evans JC, et al. Early onset seizures and Rett-like features associated with mutations in CDKL5. *Eur J Hum Genet* 2005;13:1113–20.
3. Mei D, et al. Xp22.3 genomic deletions involving the CDKL5 gene in girls with early onset epileptic encephalopathy. *Epilepsia* 2010;51:647–54.
4. Nemos C, et al. Mutational spectrum of CDKL5 in early-onset encephalopathies: a study of a large collection of French patients and review of the literature. *Clin Genet* 2009;76:357–71.
5. Russo S, et al. Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. *Neurogenetics* 2009;10:241–50.

For specific collection, transport, and testing information, refer to CDKL5-Related Disorders (CDKL5) Sequencing and Deletion/Duplication (2004935) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Familial Adenomatous Polyposis, APC Sequencing and Deletion/Duplication, and MUTYH 2 Mutations

For diagnostic or presymptomatic testing for familial adenomatous polyposis, attenuated FAP, Turcot syndrome, Gardner syndrome, and *MUTYH*-associated polyposis

## Disease Overview

- Colorectal cancer is the third most common form of cancer in the United States; individuals have a 6 percent lifetime risk of developing this disease.
- Most colorectal cancer is caused by somatic mutations and is not hereditary.
- *APC* is a tumor-suppressor gene. *APC* mutations may cause the following disorders: familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome, all of which predispose individuals to colon cancer.
- FAP is characterized by the development of hundreds to thousands of adenomatous colonic polyps, usually beginning during early adolescence (7–36 years). Without a preventative colectomy, all individuals with FAP will develop colon cancer during their lifetime, with a mean diagnosis age of 39.
- Additional characteristics of FAP may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).
- Attenuated FAP differs from FAP in that affected individuals typically have 10–100 (average of 30) more proximally located polyps, and cancer generally occurs at a later age than for individuals with FAP.
- Gardner syndrome occurs in 20 percent of families with classic FAP and is associated with benign osteomas, desmoid tumors, and soft-tissue tumors.
- Turcot syndrome consists of colon polyps and central nervous system (CNS) tumors. Turcot syndrome associated with medulloblastoma is often caused by *APC* mutations, while Turcot with glioblastoma multiforme is usually caused by mismatch repair gene mutations.
- *MUTYH*-associated polyposis (MAP) is associated with 10–100 polyps, with an age of onset in the third decade or later.

## Epidemiology

- FAP accounts for less than 1 percent of colorectal cancer cases.
- Approximately 1 percent of Caucasians are predicted to carry an *MUTYH* mutation.

## Genetics

- Inheritance is autosomal dominant for *APC*-associated polyposis; 25 percent of cases are de novo.
- Penetrance of classic FAP is 100 percent in untreated individuals.
- Sequencing will detect approximately 90 percent of *APC* mutations; large deletion/duplication analysis is necessary to detect 10 percent of *APC* mutations.
- *MUTYH*-associated polyposis (MAP) is inherited in an autosomal recessive fashion and occurs due to biallelic mutations in the *MUTYH* (formerly *MYH*) gene.

- Approximately 20–30 percent of patients with 10–100 polyps have biallelic *MUTYH* mutations.
- Two *MUTYH* mutations, Y165C and G382D, account for 85 percent of MAP in Caucasians.

## Indications for Ordering

- Confirmation of a clinical diagnosis of FAP, attenuated FAP, Gardner syndrome, Turcot syndrome, or MAP.
- Individuals at risk for an *APC*-associated polyposis or MAP due to family history but without a known familial mutation.

## Additional Ordering Notes

- For optimal test interpretation, please complete the FAP Patient Information Form and submit with the sample.

## Contraindications

- Prenatal testing.
- If testing relatives for a known familial *APC* mutation, please order Familial Mutation, Targeted Sequencing (ARUP test code 2001961).

## Interpretation

- Identification of a single pathogenic mutation in the *APC* gene is predictive of FAP or *APC*-associated polyposis.
- Detection of two *MUTYH* mutations on opposite chromosomes is predictive of MAP. *MUTYH* sequencing is recommended for symptomatic individuals with only one identifiable *MUTYH* mutation.
- A negative result does not rule out FAP, *APC*-associated polyposis, or MAP due to the possibility of an undetectable mutation in the specific gene(s) analyzed or a mutation in another gene. *MUTYH* gene sequencing should be considered in this case.
- An uncertain result means that although a gene mutation was detected, it is unknown whether it is pathogenic or benign. Medical management should rely on clinical findings and family history.

## Methodology

- Bidirectional sequencing of the entire coding region and intron-exon borders of the *APC* gene. Analytical sensitivity and specificity are 99 percent.
- Multiplex ligation-dependent probe amplification (MLPA) is performed to detect large deletions/duplications in the *APC* gene. Analytical sensitivity and specificity are 90 percent.
- Two *MUTYH* mutations, Y165C and G382D, are tested by PCR followed by fluorescence monitoring. Analytical sensitivity and specificity are approximately 99 percent. Clinical sensitivity for MAP is 85 percent in Caucasians.

## Familial Adenomatous Polyposis, APC Sequencing and Deletion/Duplication, and *MUTYH* 2 Mutations, continued

### Limitations

- Deep intronic or regulatory region mutations in the *APC* gene will not be identified.
- *APC* variants of uncertain significance may be detected.
- *APC* breakpoints of large deletions/duplications will not be determined.
- Only two targeted *MUTYH* mutations, Y165C and G382D, will be tested.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.

### Related Tests

- Familial Adenomatous Polyposis (*APC*) Sequencing (2004863)
- Familial Adenomatous Polyposis (*APC*) Deletion/Duplication (2004920)
- Familial Mutation, Targeted Sequencing (2001961)

### References

1. GeneTests: *APC*-Associated Polyposis Conditions. <http://www.genetests.org> (accessed on April 5, 2011).
2. Half E, et al. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009;4:22.
3. Lindor NM, et al. Concise handbook of familial cancer susceptibility syndromes, 2nd ed. *J Natl Cancer Inst Monogr* 2008;38:1–93.

For specific collection, transport, and testing information, refer to Familial Adenomatous Polyposis Panel, *APC* Sequencing and Deletion/Duplication, *MUTYH* 2 Mutations (2004915) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Narcolepsy (*HLA-DQB1*) Genotyping

To provide supporting evidence for diagnosis of narcolepsy in a symptomatic individual

## Disease Overview

- Narcolepsy is a sleep disorder characterized by invalidating excessive daytime sleepiness and cataplexy (the sudden loss of muscle tone triggered by strong emotions). Additional sleep abnormalities seen in individuals with narcolepsy include disturbed nighttime sleep, sleep paralysis, and hypnagogic hallucinations (occurring in the period between sleep and wakefulness).
- Narcolepsy is generally diagnosed in adulthood but has been reported in children.
- *HLA-DQB1\*06:02* is strongly associated with narcolepsy, but the *HLA-DQB1\*06:02* allele by itself is not sufficient to cause narcolepsy.

## Epidemiology

- Approximately one in 2,000 individuals is affected with narcolepsy.
- The incidence of *HLA-DQB1\*06:02* varies by ethnicity but appears important for the development of narcolepsy across all populations.

## Genetics

- Narcolepsy is multi-factorial, having both a genetic and environmental component; familial cases are rare.
- More than 99 percent of Caucasians with narcolepsy and cataplexy have the *HLA-DQB1\*06:02* allele, compared to 15–25 percent of the general Caucasian population.
- *HLA-DQB1\*06:02* is also strongly associated with narcolepsy in Japanese, African-American, Korean, and Hispanic populations.

## Indications for Ordering

- Individuals with a clinical diagnosis of narcolepsy.
- Individuals with an uncharacterized sleep disorder.

## Contraindication for Ordering

- Prenatal testing.

## Interpretation

- Identification of the *HLA-DQB1\*06:02* allele is supportive of a clinical diagnosis of narcolepsy but does not by itself establish a diagnosis.
- If the *HLA-DQB1\*06:02* allele is not identified, a diagnosis of narcolepsy is reduced but not eliminated.

## Methodology

- PCR with melting-curve analysis.
- Clinical sensitivity and specificity are 85–95 percent and less than 1 percent, respectively.

## Limitations

- This test will not differentiate between heterozygosity (one copy) and homozygosity (two copies) of the *HLA-DQB1\*06:02* allele.
- Rare diagnostic errors may occur due to primer-site mutations.
- Alleles other than *HLA-DQB1\*06:02* will not be identified.
- Other genetic and non-genetic factors that influence narcolepsy are not evaluated.

## Related Tests

- CBC with Platelet Count & Automated Differential (0040003)
- Glucose, Plasma or Serum (0020024)
- Drug of Abuse 9 Panel, Urine-Screen Only (0090453)
- Drug Screen (non-forensic), Urine, Qualitative (0090500)
- Melatonin (0098816)

## References

1. Hor, et al. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. *Nat Genet* 2010;42:786–90.
2. Mignot, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet* 2001;68:686–99.
3. Watson, et al. Does narcolepsy symptom severity vary according to *HLA-DQB1\*06:02* allele status? *Sleep* 2010;33:29–35.
4. Roh, et al. Association of HLA-DR and -DQ genes with narcolepsy in Koreans. *Hum Immunol* 2006;67:749–55.

For specific collection, transport, and testing information, refer to Narcolepsy (*HLA-DQB1\*06:02*) Genotyping (2005023) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication

DNA testing to diagnose OTC deficiency

## Disease Overview

- Ornithine transcarbamylase (OTC) deficiency is the most common of the urea-cycle disorders. The urea cycle is the body's primary system for removing waste nitrogen produced from the metabolism of protein and other nitrogen-containing molecules. Defects in the urea cycle can lead to life-threatening accumulations of ammonia.
- Waste nitrogen is converted to ammonia and then transferred to the liver for processing via the urea cycle. OTC is one of the proximal enzymes in the urea cycle and converts carbamylphosphate and ornithine to citrulline. The more distal enzymes in the urea cycle use citrulline as a substrate to produce urea, which is then excreted.
- Classic OTC deficiency is characterized by hyperammonemia, cyclical vomiting, seizures, lethargy, coma, and neonatal death if not treated.
- Males with OTC deficiency are typically severely affected, with onset of symptoms occurring in the first few days of life. Some males with OTC deficiency may show only mild symptoms with adult onset of disease.
- Females can have variable clinical presentations ranging from completely asymptomatic to classic, life-threatening neonatal disease. Approximately 15 percent of female carriers of OTC deficiency develop hyperammonemia at some point in their lives due to skewed X-inactivation.
- A diagnosis of OTC deficiency is suspected in symptomatic individuals with elevated plasma ammonia levels, low plasma citrulline and arginine concentration, and elevated urine orotic acid levels.
- Treatment of OTC deficiency includes reducing plasma ammonia concentration with dialysis, administering nitrogen scavengers to allow excretion of excess nitrogen via alternative pathways, reducing protein in the diet, providing calories through carbohydrates and fat to reduce catabolism, and reducing the risk of neurological damage during stabilization with administration of IV fluids. In severe cases, liver transplantation may be considered.

## Epidemiology

- Incidence is approximately one in 14,000 births in the United States.

## Genetics

- X-linked inheritance.
- OTC is the only gene associated with OTC deficiency.
- De novo mutation rate is unknown but may vary by gender. Females with a mutation may be more likely than males to have a sporadic mutation.

## Indications for Ordering

- Diagnostic testing for individuals with clinical and/or biochemical evidence of OTC deficiency.
- Carrier testing for female relatives of an individual with OTC deficiency.

## Contraindication for Ordering

- Prenatal testing.

## Additional Ordering Notes

- If there is a family history of OTC deficiency and the specific familial mutation has already been identified, testing can be performed on at-risk family members by contacting ARUP's genetic counselor and requesting targeted sequencing for the familial mutation.

## Interpretation

- One copy of a pathogenic OTC mutation in males predicts OTC deficiency.
- Females with one copy of a pathogenic mutation have variable presentations that range from asymptomatic to classic, life-threatening disease.
- When no pathogenic mutations are detected by sequencing and deletion/duplication analysis, the possibility that the individual is a carrier of or affected with OTC deficiency is reduced. Medical management should rely on clinical findings.
- OTC mutations of unknown clinical significance may be detected by this assay.

## Methodology and Limitations

- PCR followed by bidirectional sequencing of the entire coding region and intron-exon boundaries of the OTC gene.
- Multiplex ligation-dependent probe amplification (MLPA) to identify large exonic deletions/duplications in the OTC gene.
- Combined clinical sensitivity for sequencing and deletion/duplication analysis is up to 90 percent. Approximately 80 percent of detectable mutations are sequence variants, while up to 10 percent of causative mutations are large deletions.
- Analytical sensitivity and specificity are 99 percent.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Regulatory region mutations and deep intronic mutations will not be detected. Breakpoints of large deletions/duplications will not be determined.
- Genes associated with urea cycle disorders, other than OTC, will not be evaluated.

## Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication, continued

### Related Tests

- Amino Acids Quantitative, Plasma (0080710)
- Orotic Acid, Urine (0092458)

### References

1. GeneTests: Urea Cycle Disorders Overview. [www.genetests.org](http://www.genetests.org) (accessed on November 29, 2010).
2. Summar ML. Urea cycle disorders. In *Pediatric endocrinology and inborn errors of metabolism*. K Sarafoglou, GF Hoffman, KS Roth, eds. 2009; New York: McGraw-Hill.
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4. Tuchman M, et al. Mutations and polymorphisms in the human ornithine transcarbamylase gene. *Hum Mutat* 2002;19(2):93–107.

For specific collection, transport, and testing information, refer to Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication (2004896), Ornithine Transcarbamylase Deficiency (OTC) Sequencing (2004901), and Ornithine Transcarbamylase Deficiency (OTC) Deletion/Duplication (2004892) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Paroxysmal Nocturnal Hemoglobinuria Panel

For diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria (PNH)

## Test Highlights

- This panel has two separate flow cytometric assays that detect PNH in white blood cells (WBC) and red blood cells (RBC).
- The five-color PNH WBC and the two-color PNH RBC flow assay detect the loss of glycosyl phosphatidylinositol (GPI) anchoring proteins (GPI-AP), which are diagnostic of PNH.
- This panel (testing of WBCs and RBCs simultaneously) is recommended for initial diagnosis, but each assay is available individually. Determination of PNH clone size is best made by quantifying the percentage of GPI-AP-deficient WBCs, while the type of PNH cells (i.e., type I, type II, and type III) is best determined by analyzing RBCs.

## Disease Overview

- PNH is a rare acquired hemolytic disorder caused by a nonmalignant clonal expansion of one or more stem cell lines.
- Clinical presentation:
  - Chronic hemolysis and hemoglobinuria.
  - Symptoms of anemia (i.e., fatigue, pallor, and weakness).
  - Thrombophilia (occurs in up to 40 percent of patients)
    - Thromboses at unusual sites, particularly abdominal veins, including hepatic vein thrombosis (Budd-Chiari syndrome) may complicate PNH. Cerebral vein thrombosis may also complicate PNH.
    - Thrombosis is the leading cause of death in PNH.
  - Bone marrow failure (PNH may complicate aplastic anemia).
  - Other signs and symptoms may include dysphagia, abdominal pain, iron deficiency, jaundice, smooth muscle dysfunction, and male impotence.

## Epidemiology

- Incidence is 1.3:1,000,000.
- Median age of onset is 40 years.
- Males and females are equally affected.

## Pathophysiology

- Acquired mutation of the *PIGA* gene in one or more hematopoietic stem cells results in the deficiency or absence of GPI-anchored cell membrane proteins on progeny of the affected stem cell(s).
- RBC sensitivity to complement lysis occurs due to deficiency of GPI-anchored membrane proteins that regulate complement.
- Pathophysiology of bone marrow failure and thromboses is not known.
- Approximately 60 percent of patients with acquired aplastic anemia have detectable PNH cells.
- A subclinical PNH population in aplastic anemia or other bone marrow failure disorder may correlate with a positive immunotherapeutic response.

## Indications for Ordering

- Unexplained hemoglobinuria.
- Coombs-negative hemolytic anemia.
- Unusual presentation of thrombosis (Budd-Chiari syndrome or cerebral thrombosis).
- Coexistent thrombosis and intravascular hemolysis or cytopenias.
- Aplastic or hypoplastic anemia.

## Interpretation

- PNH cells  $\geq 1$  percent in WBCs and RBCs indicates PNH.
- RBC PNH cells  $\geq 0.005$  percent but less than 1 percent indicates subclinical PNH, often associated with bone marrow failure syndromes.
- Assay sensitivity is 0.1 percent for WBCs and 0.005 percent for RBCs; results below these limits are normal.

## Limitations

- Very neutropenic samples may not have enough cells for accurate WBC analysis.
- Gross hemolysis or samples that lack CD15, CD33, or glycoporphin A expression will compromise accuracy.
- Recent RBC transfusions may compromise accuracy.

## Methodology

- WBCs and RBCs are analyzed by flow cytometry.
- WBCs are stained using a panel of five markers. CD15 and CD33 expression are used as lineage-specific markers for granulocytes and monocytes, respectively. Reductions in CD14 on monocytes and CD24 expression on granulocytes, along with low FLAER binding, are used to identify PNH cells.
- RBCs are stained with glycoporphin A as a lineage-specific marker and CD59 to identify PNH cells. If the RBC PNH cells are  $\geq 1$  percent, the fraction of type II and type III cells is also reported.

## Related Tests

- Paroxysmal Nocturnal Hemoglobinuria Profile—Red Blood Cells (2004366)
- Paroxysmal Nocturnal Hemoglobinuria Profile—White Blood Cells (2005003)

## References

1. Borowitz MJ, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry B Clin Cytom* 2010;78:211–30.
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4. Brodsky RA. Advances in the diagnosis and therapy of paroxysmal nocturnal hemoglobinuria. *Blood Rev* 2008;22:65–74.

For specific collection, transport, and testing information, refer to Paroxysmal Nocturnal Hemoglobinuria Panel, RBC and WBC (2005006) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# PIK3CA Mutation Detection by Pyrosequencing

For helping predict patient prognosis and therapeutic response in many cancers, including those of the colon, ovary, breast, brain, liver, and leukemia

## Test Highlights

- The majority (~80 percent) of somatic mutations in *PIK3CA* are located in three hotspots: two in exon 9 in the helical domain of codons 542 and 545 and one in codon 1047 in the exon 20 kinase domain.<sup>1</sup>
- *PIK3CA* mutational status may indicate a tumor that will respond to drugs targeted at genes downstream of *PIK3CA* in the AKT/mTOR-signaling cascade.<sup>2</sup>
- Mutations in exon 20 of this gene can also inhibit therapeutic response to EGFR-targeted therapies in patients with metastatic colorectal cancer.<sup>3</sup>
- This test excludes interference from a pseudogene on chromosome 22 with >95 percent homology to *PIK3CA*.

## Disease Overview

- In the United States, colorectal cancer is the third most common form of cancer; individuals have a 6 percent lifetime risk of developing this disease.
- Most cancer is caused by somatic mutations and is not hereditary.
- Somatic mutations in *PIK3CA* occur in up to 30 percent of common epithelial cancer, which includes breast, colon, prostate, and endometrial cancers.<sup>4</sup>

## Indications for Ordering

- *PIK3CA* exon 20 mutations may indicate a tumor that will not respond to anti-EGFR therapies (as in colon cancer).
- *PIK3CA* mutations may indicate a tumor that will respond to drugs targeted at genes downstream of *PIK3CA* in the AKT/mTOR-signaling cascade.
- *PIK3CA* mutations are associated with a significant increase in colon cancer-specific mortality and shorter breast cancer-specific and disease-free survival.<sup>5,6</sup>

## Interpretation

- The presence of an oncogenic mutation in codons 542, 545, and 1047 of *PIK3CA* is indicative of a tumor that may respond to drugs targeted at genes downstream of *PIK3CA* in the AKT/mTOR-signaling cascade.
- Mutations in exon 20 of this gene may also indicate tumors (e.g., metastatic colorectal cancer) that will not respond to EGFR-targeted therapies.

## Methodology

- Tumor tissue is microdissected and DNA extracted from five micron sections of formalin-fixed, paraffin-embedded tissue blocks.
- Regions covering codons 542, 545, and 1047 of the *PIK3CA* gene are amplified using polymerase chain reaction (PCR), followed by pyrosequencing.
- All potentially oncogenic mutations in codons 542, 545, and 1047 are detected.
- Limit of detection for this assay is 10 percent mutant alleles.

## Limitations

- Mutations in other locations within the *PIK3CA* gene or in any other gene will not be detected.
- Absence of *PIK3CA* mutations does not guarantee a positive response to anti-EGFR therapies in metastatic colorectal cancer.
- Presence of mutations in codons 542, 545, and 1047 does not guarantee a positive response to therapies targeted to the AKT/mTOR-signaling cascade.

## References

1. Ligresti G, et al. *PIK3CA* mutations in human solid tumors: role in sensitivity to various therapeutic approaches. *Cell Cycle* 2009;8(9):1352-8.
2. Di Nicolantonio F, et al. Deregulation of the PI3K and KRAS signaling pathways in human cancer cells determines their response to everolimus. *J Clin Invest* 2010;120(8):2858-66.
3. De Roock W, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010;11(8):753-62.
4. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer* 2009;9(8):550-62.
5. Aleskandarany MA, et al. PIK3CA expression in invasive breast cancer: a biomarker of poor prognosis. *Breast Cancer Res Treat* 2010;122(1):45-53.
6. Ogino S, et al. PIK3CA mutation is associated with poor prognosis among patients with curatively resected colon cancer. *J Clin Oncol* 2009;27(9):1477-84.

For specific collection, transport, and testing information, refer to *PIK3CA* Mutation Detection (2004510) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Plasminogen Activator Inhibitor-1, PAI-1 (*SERPINE1*) Genotype

To assess genetic risk for thrombosis-associated PAI-1 activity

## Disease Overview

- Plasminogen activator inhibitor (PAI-1), or serpin peptidase inhibitor, is an inhibitor of fibrinolysis.
- PAI-1 inhibits tissue-type (t-PA) and urokinase (uPA) plasminogen activator. PAI-1 stimulates interstitial macrophage recruitment and increases transcription of profibrotic genes. PAI-1 is also important for signal transduction, cell adherence, and migration.
- PAI-1 acts as an acute-phase protein in acute inflammation and is important in the pathogenesis of sepsis. Increased levels of PAI-1 are correlated with increased severity of disease, increased levels of various cytokines, acute-phase proteins, and coagulation parameters.
- PAI-1 levels are regulated by metabolic factors, such as triglycerides, cholesterol, and insulin.
- The single guanosine nucleotide deletion/insertion polymorphism (4G/5G) at -675 bp of the *SERPINE1* gene is the major genetic determinant of PAI-1 expression. The PAI-1 promoter 4G allele, compared to 5G allele, is associated with increased PAI-1 transcription activity, higher PAI-1 plasma levels, and reduced fibrinolysis.

## Epidemiology

- Allele frequency for the 4G allele is 0.52 in Caucasians, 0.38 in Hispanics, and 0.13–0.28 in African-Americans.

## Genetics

- Autosomal dominant inheritance.
- The 4G/5G insertion/deletion polymorphism is located in the promoter region of the *SERPINE1* gene, c.-148-672, on chromosome 7q 21.3-q 22.
- The molecular mechanism for the 4G allele-mediated higher PAI-1 expression is associated with greater binding of upstream stimulatory factor-1 to the E-box adjacent to the 4G site (E-4G) than to the E-5G.
- Individuals with 4G/5G and 4G/4G genotypes, especially those with other thrombophilic risk factors, are at increased risk for venous thromboembolism (VTE).
- Both the 4G/5G and 4G/4G genotypes are also associated with increased risk of myocardial infarction (MI).
- Some studies have associated the 5G/5G genotype with elevated risk of ischemic stroke (IS), along with decreased PAI-1 transcription in brain astrocytes and lower PAI-1 activity levels compared to the 4G/4G genotype.

## Indications for Ordering

- To assess genetic susceptibility for VTE or MI in individuals with a personal or family history of thrombotic events.
- Risk-benefit assessment for preventive or therapeutic interventions for VTE or MI.

## Contraindication

- Fetal testing.

## Interpretation

- 5G/5G genotype: Two copies of the *PAI-1* 5G allele were detected.
- 4G/5G genotype: One copy of the 4G allele was detected; this result is associated with an increased risk for VTE and MI.
- 4G/4G genotype: Two copies of the 4G allele were detected; this result is associated with an increased risk for VTE and MI.
- Results of 4G/5G *PAI-1* genotyping should be interpreted in the context of other laboratory tests and clinical information. Thrombotic risk may be altered by other genetic and non-genetic factors not assessed by this assay.

## Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect the *PAI-1* 4G/5G genotype, c.-148-672.
- Analytical sensitivity and specificity are 99 percent.

## Limitations

- Variants in the *SERPINE1* gene, other than the 4G/5G, are not evaluated.
- Rare diagnostic errors may occur due to primer-site mutations.

## Related Tests

- Thrombotic Risk, DNA Panel (0056200)
- Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden (0030133)
- Thrombotic Risk (Acquired) Reflexive Panel (0030268)
- Prothrombin (*F2*) G20210A Mutation (0056060)
- Factor V Leiden (*F5*) R506Q (0097720)
- Plasminogen Activator Inhibitor1, Activity (0098781)
- Methylenetetrahydrofolate Reductase (*MTHFR*) 2 Mutations (0055655)

## Plasminogen Activator Inhibitor-1, PAI-1(*SERPINE1*) Genotype, continued

### References

1. Bentley P, et al. Causal relationship of susceptibility genes to ischemic stroke: comparison to ischemic heart disease and biochemical determinants. *PLoS One* 2010;5:e9136.
2. Boekholdt SM, et al. Genetic variation in coagulation and fibrinolytic proteins and their relation with acute myocardial infarction: a systematic review. *Circulation* 2001;104:3063–8.
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For specific collection, transport, and testing information, refer to Plasminogen Activator Inhibitor -1, PAI-1 (*SERPINE1*) Genotyping (2004980) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

# Voltage-Gated Potassium Channel (VGKC) Autoantibody Testing

For the diagnosis of peripheral nerve hyperexcitability, limbic encephalitis, autonomic involvement, or Morvan syndrome

## Test Highlights

- Autoantibodies against voltage-gated potassium channels (VGKC) may cause hyperexcitability of the peripheral and central nervous systems and are detected by radioimmunoassay (RIA). These antibodies may be associated with paraneoplastic or non-paraneoplastic (autoimmune) neurologic disorders.

## Disease Overview

- Autoantibodies that recognize the voltage-gated potassium channels found at the neuromuscular junction (Kv 1.1, Kv 1.2, and Kv 1.4) have been identified in a spectrum of diseases. Peripheral nerve hyperexcitability resulting in muscle twitching, muscle cramps, and stiffness has been referred to by a variety of names, including neuromyotonia (NMT), Isaac syndrome, undulating myokymia, and cramp-fasciculation syndrome.
- A similar condition with additional symptoms of pain, excessive sweating, sleep disorders (i.e., insomnia, abnormal rapid eye movement), delirium, and cardiac arrhythmia was first described by the French physician Augustin Marie Morvan in 1890 and has been referred to as Morvan fibrillary chorea and Morvan syndrome.
- Autoantibodies that recognize voltage-gated potassium channels in the central nervous systems (Kv 1.1, Kv 1.2, and Kv 1.6) have been detected in association with limbic encephalitis, frontotemporal dementia-like syndrome, and amnesia.
- Definitive differentiation among these diseases is problematic due to the presence of antibodies to proteins closely associated with the neuronal VGKC complex that may be precipitated in VGKC RIA assays. This may explain the variety of limbic encephalitis immunophenotypes, not all of which are associated with VGKC antibodies.
- NMT is a diverse family of disorders that may be confused with early stages of amyotrophic lateral sclerosis (ALS) characterized by muscle fasciculation and muscle weakness. It is critical to differentiate among these diseases since ALS demonstrates a fatal prognosis whereas NMT is rarely fatal.
- Palliative treatment of NMT usually consists of anticonvulsants, immunosuppressive therapy, or plasmapheresis.

## Epidemiology

- Insufficient data is available regarding the incidence and prevalence of anti-VGKC antibodies.
- Generalized peripheral nerve hyperexcitability and NMT are divided into three categories: acquired, paraneoplastic, and hereditary, with the majority of cases classified as acquired.
- Both autonomic and central nervous system involvement are present in Morvan syndrome.
- Limbic encephalitis has been classified into three categories: VGKC antibody-associated, paraneoplastic, and idiopathic; it may be monophasic or relapsing/recurrent in nature.

## Indications for Ordering

- Confirmation of acquired neuromyotonia and Morvan syndrome.
- Assessment and prognosis of limbic encephalitis.
- Differential diagnosis of other neuromuscular disorders (i.e., myasthenia gravis, Lambert-Eaton syndrome), paraneoplastic syndromes, neurological disorders, and autoimmune neuropathological syndromes.

## Interpretation

- Negative: 0–31 pmol/L.
- Indeterminant: 32–87 pmol/L.
- Positive: >88 pmol/L.
- The presence of VGKC antibodies should be used in conjunction with clinical manifestations and proposed diagnostic criteria for the neuromyotonia spectrum of disorders and VGKC antibody-associated limbic encephalitis; it should not be used as the sole criteria for diagnosis.

## Limitations

- A sensitivity of 40–83 percent is reported for VGKC antibody detection by radioimmunoassay (RIA) assays using 125-iodine conjugated alpha-dendrotoxin labeled voltage-gated potassium channels.
- Antibodies detected are isotype-restricted to IgG immunoglobulin.
- VGKC receptor complex proteins may be co-precipitated by anti-VGKC antibodies, including leucine-rich, glioma inactivated 1 protein (LGI1), and contactin-associated protein 2 (Caspr-2).

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1. Hart IK, et al. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002;125:1887–95.
2. Liguori R, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001;124:2417–26.
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For specific collection, transport, and testing information, refer to Voltage-Gated Potassium Channel (VGKC) Antibody (2004890) on the ARUP website at [www.aruplab.com](http://www.aruplab.com). For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).



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