

Medical Testing of Some Inherited Disorders for Families who have Suffered a Sudden Unexplained Death

Families who have experienced the sudden unexplained death of their baby or child often ask, "Should I have my other children tested?" This important question may be followed by the response of "Test them for what?" At this time, we do not know how to predict or prevent SIDS/SUDC. However, we do know that some rare inheritable disorders can cause sudden unexpected death. We also know that death investigations, as well as state mandated newborn screenings, vary across the U.S. Therefore, it is difficult to recommend one specific set of tests for all families who have suffered an unexplained childhood death.

As with research about SUDC, research in the area of inherited disorders continues. The ability to diagnose and treat individuals with these conditions continues to save lives and maximize the health of those affected. Without diagnosis and treatment, disorders such as Long QT Syndrome and various metabolic disorders would continue to be the cause of sudden unexpected deaths in children and some adults.

Researchers involved with the SUDC Research Project were asked about family testing issues. Recommendations for every family member include following optimal pediatric care recommendations, attending well child visits, maintaining current vaccinations, and obtaining appropriate health care when clinically indicated.

In addition, the following information includes tests appropriate for consideration in families who have suffered the sudden loss of a child where the cause of death is unknown or unclear. Sharing them with your doctor or your child's pediatrician should be helpful in designing a specific testing plan for your present family members, as well as for future pregnancies and subsequently born children. Your doctor or pediatrician may recommend other tests in addition to the following, based on your specific family history and the circumstances and information known regarding the child who died.

With continued research, we hope that this list will be further refined to provide the best care and hope for the future of all families.

Evaluating Inborn Errors of Metabolism:

During the PRENATAL period:

Get regular and early prenatal care.

Special consideration should be given to the possible occurrence of maternal complications: Acute fatty liver of pregnancy (AFLP); Hemolysis, Elevated Liver (enzymes), Low Platelets Syndrome (HELLP); pre-eclampsia, and others

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For the Asymptomatic SUDC Sibling NEWBORN:

Blood

Expanded newborn screening by MS/MS (blood spots)—If this is not mandated in your state, bloodspot cards can be requested ahead of time from private labs. (Information on some available labs can be obtained from the SUDC Program.)

Urine

Organic Acids

For the Symptomatic SUDC Sibling NEWBORN:

If the newborn is not well — Seek medical attention immediately.

Start evaluation with investigations that include:

Blood Gases, glucose, electrolytes, Lactate, pyruvate, Ammonia

Urine- Organic Acids

For Older Siblings:

PLASMA acylcarnitines and Urine organic acids

If expanded newborn screening, plasma acylcarnitines and organic acids are negative, the pursuit of additional targeted tests should be considered on a case-by-case basis, also determined by the outcome of the postmortem investigation in the child who died suddenly.

References for metabolic testing:

Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. *Ann Rev Physiol* 64:16.1-26, 2002.

Bennett MJ, Rinaldo P. The Metabolic Autopsy comes of Age. *Clinical Chemistry* 47; 1145-6, 2001

Tortorelli S, Hahn SH, Cowan TM, Brewster TG, Rinaldo P, Matern D. The urinary excretion of glutarylcarnitine is an informative tool in biochemical diagnosis of glutaric acidemia type 1. *Molecular Genetics and Metabolism* 84:137-143, 2005

Mayo Medical Laboratories Communiqué on postmortem testing

<http://www.mayomedicallaboratories.com/media/articles/communique/mc2831-0903.pdf>

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Evaluating Cardiac Mechanisms:

1. A VERY careful and detailed medical history of the decedent with review of the autopsy report and sometimes the autopsy tissue itself
2. A VERY careful and thorough review of the family history with pedigree analysis on both sides searching for the "needles in a haystack"

If anything is suggestive of a possible cardiac mechanism: screen siblings and parents with an electrocardiogram (EKG or ECG) and an echocardiogram (ECHO). Long QT Syndrome (LQTS) is a disorder of the electrical system of the lower chambers of the heart (ventricles) and just one type of inheritable disorder.

What is Long QT Syndrome (LQTS)?

By Michael J. Ackerman, MD, PhD

Long QT **Syndrome** (LQTS) is a disorder of the electrical system of the lower chambers of the heart (ventricles). The mechanical or pumping function of the heart is normal. However, the recharging (repolarization) system of the heart is either slow, taking longer than normal to recharge, or inefficient (disorganized). LQTS can be divided into two broad categories: congenital and acquired. In **acquired** LQTS, the electrical recharging abnormality is secondary to medications, abnormalities in electrolytes, or other illnesses (like anorexia nervosa for example) that prolong the QT interval. In contrast, **congenital** LQTS is known as a primary cardiac ion channel disease due to mutations in the genes encoding the proteins (ion channels) responsible for this electrical recharging process. It is estimated that 1 in 3000 persons may have congenital LQTS. The symptoms of LQTS vary tremendously from NO symptoms ever (about 40-50%) to fainting/seizure spells (40-50%) in the setting of exercise like swimming, auditory startles (alarm clocks, phone, doorbells) to sudden death (5-10%). Since the heart's structure and mechanical performance is normal in LQTS, there are no clues found at autopsy. In fact, LQTS should be considered strongly for any sudden unexplained death accompanied by a normal autopsy. An estimated 5 – 15% of sudden infant death syndrome may be caused by LQTS-causing genetic defects. In a postmortem investigation of SUD victims where the average age was 14 years, 20% of the decedents were found to have mutations in LQTS genes. Based upon this data, it is strongly recommended that a careful family history be obtained and screening electrocardiograms of first degree relatives (parents, children, siblings) be considered in the setting of a sudden unexplained and autopsy negative death. Postmortem genetic testing of DNA from the decedent should become the standard of care in the evaluation of SUD but this is hindered presently by the cost of genetic testing and the apparent reluctance of health insurance companies to reimburse for such diagnostic testing despite the potential life saving, not to mention cost saving, benefit for the loved ones left behind.

Screening test in a newborn: Importantly, if a newborn ECG is suggestive of long QT syndrome, it must be repeated as the false positive rate may be high in the first week of life. If the ECG is persistently abnormal at the 2nd week and/or 2 month well child visit, then strong consideration for the diagnosis of long QT syndrome must be given.

In addition, an epinephrine QT stress test (performed in individuals > 10 years) may unmask long QT syndrome. If directed by results of such investigations, molecular genetic testing for a "cardiac channelopathy" like long QT syndrome should be pursued.

Commercial testing for the 5 Long QT Syndrome genes is available - www.familion.com (1-866-familion).

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Postmortem genetic testing is not likely to be reimbursed right now - and could cost \$5400. Postmortem genetic testing will continue on a research level, where tissue is studied without a financial burden.

Genetic Testing for RyR2 mutations (in 3rd reference below) is NOT commercially available and can only be done through a research lab at the present time.

Current research has found a greater incidence of channelopathies diagnosed postmortem with the greater age of the child. Especially with greater age, and when the decedent's autopsy fails to demonstrate any structural abnormalities, then consider the clinical screen for survivors to rule out or assess for the possibility of inherited heart rhythm syndromes.

Clinical screening tests would include: a. ECG/EKG, b. Holter, and c. Exercise Stress Test (Exercise stress test recommendation is based on the findings and recommendations of the 3rd reference below, due to CPVT escaping detection by a resting electrocardiogram).

Any additional provocative tests (i.e epinephrine QT stress test, procainamide stress test, or isoproterenol stress test, or diagnostic EP study) would be based upon the clinical impression, family history, etc.

Evaluation of Long QT Syndrome (LQTS) Today: Options through Research and Commercial Testing

Today, two options exist as set forth below. Both have their pros and cons. Discuss these options with your Doctor so you can come to the best decision for your particular family.

1. **Commercial**, clinical LQTS genetic testing via FAMILION (www.familion.com),
Length of time from testing to results: about 4 - 6 weeks,
Participation requires blood in EDTA, and costs \$5400.
*FYI: Postmortem genetic testing is so far unlikely to be paid for by insurance.

2. **Research** genetic testing in Mayo Clinic's Sudden Death Genomics Laboratory –
IRB-approved, free, and consent of appropriate next of kin is required. Here, the focus is on discovery and the research subject's specific "service" is a hoped for result with successful elucidation of novel causes for sudden unexplained death.
Length of time from testing to results: SLOW! Usually more than one year. In general, contact with the medical examiners and families only occur in the event that the research testing identifies a probable genetic cause. Participation: Requires DNA from deceased that is adequate for testing (i.e., frozen tissue that is DNA rich, blood in EDTA, blood spot cards).

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In general, formalin fixed tissue and paraffin-embedded tissue will NOT permit a successful molecular autopsy.

References:

Ackerman MJ, Tester DJ, Driscoll, DJ. Molecular autopsy of sudden unexplained death in the young. *The American Journal of Forensic Medicine and Pathology*. 2001; 22(2): 105-111.

Ackerman MJ, Khosiseth A, Tester DJ, Hejlik J, Shen WK, Porter CJ. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clinic Proceedings*. 2002;77:413-421.

Tester DJ, Spoon DS, Valdivia HH, Makielski JC, Ackerman MJ. Targeted Mutational Analysis of RyR2-Encoded Cardiac Ryanodine Receptor in Sudden Unexplained Death: A Molecular Autopsy of 49 Medical Examiner/Coroner Cases. *Mayo Clinical Proceedings*, 2004, 79 (11): 1380-1384 www.mayo.edu/proceedings

Evaluating Seizures

Families entering the SUDC Research Project to date are reporting a higher than expected incidence of seizures, especially febrile seizures, in the child who died and sometimes family members as well. Medical literature over the last several decades reports on the benign nature of simple febrile seizures. At this time, we recommend a neurological consultation for all SUDC siblings who have a history of seizures (febrile or without fever) or any other neurological concern (e.g., developmental delay) with a pediatric neurologist. The articles below may provide some information and guidance to families and physicians. At this time, since the association between SUDC and febrile seizures is still being investigated, we can not make any general recommendations about the specific evaluation and treatment of febrile seizures in siblings of children who have died of SUDC.

If, at any time, contact with the SUDC Program for more information and/or direct contact with our researchers or physicians would be helpful in evaluating these children, please call Laura Crandall at 800-620-SUDC.

Mazumdar, M **Febrile Seizures and Risk of Death** (editorial) *Lancet*. 2008; Vol 372:429-430.

Kinney HC, Armstrong DL, Chadwick AE, et al. **Sudden Death in Toddlers Associated with Developmental Abnormalities of the Hippocampus: a report of five cases.** *Pediatr Dev Pathol*. 2007;10(3):208-223.

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Krous HF, Chadwick AE, Crandall L, Nadeau-Manning. Sudden Unexpected Death In Childhood: A Report of the 50 Cases. Pediatric Dev Pathol. 2005 July 14

Kinney H, Armstrong DL, Chadwick AE, Crandall L, Hilbert C, Krous H. Abstract: Seizures, Cerebral Edema and Hippocampal Anomalies in Sudden Unexplained Death In Childhood (SUDC): Report of A Series. J Neuropathol Exp Neurol 2004; 63 (5):556

The SUDC Program offers the above information as a starting point for discussions with your personal doctor, who knows your family best. It is not meant to be sufficient for all families who have suffered an unexplained death due to some of the reasons mentioned at the beginning of this document.

Discuss the above with your doctor. Ask him/her to evaluate these recommendations in the context of the specific outcome of the postmortem investigation in the child who died suddenly and any pertinent family history. If additional clarification or assistance is needed for understanding or carrying out these guidelines, please contact The SUDC Program for the direct contact information of the contributing physicians.

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