THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Allan-Herndon-Dudley Syndrome Testing

Clinical Features:

Males with Allan-Herndon-Dudley syndrome [OMIM #30523], also known as *SLC16A2 (MCT8)*-specific thyroid hormone cell transporter (THCT) deficiency, syndromic X-linked mental retardation with high serum T3, and thyroid hormone cell transport defect, have severe developmental delay, gait disturbance, dystonia, and poor head control. Although death of affected males in the early teens is not uncommon, affected males have survived to old age. Hypotonia is typical in early infancy, spasticity develops in late childhood with dystonic/atetoic movements and garbled or no speech. Heterozygous carrier females have only mild thyroid hormone abnormalities but no neuropsychiatric defects (1).

Patients with this condition also have a thyroid hormone defect presenting with unusual combination of increased serum 3,3',5-triiodothyronine (T3), decreased serum thyroxine (T4) and low 3,3',5'-triiodothyronine (reverse T3, rT3) concentrations found in both males and to a lesser degree in carrier females (1). However, T3 and reverse T3 are not commonly measured and normal ranges for children are not available in routine laboratories.

Suggested minimal clinical criteria include **the following, along with an elevated T3:**

- Truncal hypotonia
- Limb spasticity
- Poor head control
- Speech and motor delays

Molecular and Biochemical Genetics:

Mutations of the *SLC16A2 (MCT8)* [OMIM #300095] gene, have been identified in patients with Allan-Herndon-Dudley syndrome (1, 2). *SLC16A2* has 6 coding exons, and more than 20 mutations have been identified. No clear genotype-phenotype correlations have been reported.

SLC16A2 is thought to play a role in neuronal T3 uptake with a deficiency resulting in an insufficient supply of T3 to nuclear T3 receptors. Thyroid hormone plays a very crucial role in brain development. Thus, it is presumed that this decreased access of T3 into neurons can lead to severe defects in neurological development (3).

Inheritance:

Allan-Herndon-Dudley syndrome is an X-linked condition resulting in clinical features in affected males. A woman who has more than one affected son is an obligate carrier. Penetrance appears to be 100%. Recurrence risk for carrier mothers is 50%. However, only males with *SLC16A2* mutations manifest neurologic symptoms.

Test methods:

Two blood samples are needed for testing. Dr. Refetoff's Endocrinology Laboratory will perform thyroid hormone tests on the red-top tube including T4, T3, reverse T3 concentrations. If the panel is normal, we will issue a report without any genetic testing. If the results are consistent with *SLC16A2*-specific THCT deficiency, samples will be analyzed for *SLC16A2* mutations. Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC16A2* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. We also offer deletion/duplication analysis of the *SLC16A2* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory. Patients with abnormal thyroid

hormone tests with or without *SLC16A2* gene mutations can enroll in Dr. Refetoff's research study (refetoff@uchicago.edu) for further studies.

Please, send a completed MCT8 Clinical Questionnaire and patient consent form with each sample.

This information will be used to aid in interpretation of the test result. The clinical data form, along with the test result, will be shared with Dr. Refetoff and stored anonymously in an *SLC16A2* database.

Tier 1: Normal thyroid testing only

Sample specifications:	3 to10cc of blood in a red top tube and 3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$350
CPT codes:	84436, 84481, 84443, 84482
Turn-around time:	2 weeks

Tier 2: *SLC16A2 (MCT8)* sequencing

Sample specifications:	3 to10cc of blood in a red top tube and 3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

SLC16A2 (MCT8) deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Dumitrescu AM, Liao XH, Best TB et al. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004: 74: 168-175.
2. Schwartz CE, May MM, Carpenter NJ et al. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. Am J Hum Genet 2005: 77: 41-53.
3. Friesema EC, Jansen J, Heuer H et al. Mechanisms of disease: psychomotor retardation and high T3 levels caused by mutations in monocarboxylate transporter 8. Nat Clin Pract Endocrinol Metab 2006: 2: 512-523.

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