

The University of Chicago Genetic Services Laboratories



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Analysis for *MCT8*-specific Thyroid Hormone Cell Transporter Deficiency

Clinical Features:

Males with *MCT8*-specific thyroid hormone cell transporter (THCT) deficiency [OMIM #30523], also known as Allan-Herndon-Dudley syndrome, *MCT8* 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/atetoid 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

All samples will undergo thyroid hormone testing in Dr. Refetoff's Endocrinology Laboratory at the University of Chicago to examine the presence of thyroid hormone abnormalities before MCT8 sequencing. To date, all patients with MCT8 abnormalities have demonstrated thyroid hormone abnormalities.

Molecular and Biochemical Genetics:

Mutations of the *MCT8* [OMIM #300095] gene, or monocarboxylate transporter 8, have been identified in patients with *MCT8*-specific THCT deficiency [1,2]. *MCT8* has 6 coding exons, and more than 20 mutations have been identified. No clear genotype-phenotype correlations have been reported.

MCT8 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:

MCT8-specific THCT deficiency 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 *MCT8* mutations manifest neurologic symptoms.

Additional Resources:

MCT8 Organization
www.mct8organization.org

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 *MCT8*-specific THCT deficiency, samples will be sequenced for *MCT8* mutations. We offer full gene sequencing of all 6 coding exons and intron/exon boundaries.

Patients with abnormal thyroid hormone tests with or without *MCT8* 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 *MCT8* database.

Normal thyroid testing only:

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|------------------------|--|
| Sample specifications: | 3 to 10cc of blood in a red top tube and 3 to 10cc of blood in a purple top (EDTA) tube |
| Cost: | \$350 |
| CPT codes: | 83891, 83912, 90001 |
| Turn-around time: | 2 weeks |

Thyroid testing and *MCT8* sequencing:

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|------------------------|--|
| Sample specifications: | 3 to 10cc of blood in a red top tube and 3 to 10cc of blood in a purple top (EDTA) tube |
| Cost: | \$1500 |
| CPT codes: | 83891, 83898 x 4, 83904 x 6, 83912 |
| Turn-around time: | 4 - 6 weeks |

Testing for a known mutation in additional family members

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|------------------------|---|
| Sample specifications: | 3 to 10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$390 |
| CPT codes: | 83891, 83898 x 2, 83894, 83912 |
| Turn-around time: | 3-4 weeks |

Prenatal testing for a known mutation

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|------------------------|--|
| Sample specifications: | 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid |
| Cost: | \$590 |
| CPT codes: | 83891, 83898 x 2, 83894, 83912, 99051 |
| Turn-around time: | 1-2 weeks |

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

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References:

1. Dumitrescu AM, et al. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene (2004) *Am J Hum Genet* 74: 168-175.
2. Schwartz CE, et al. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (*MCT8*) gene (2005) *Am J Hum Genet* 77: 41-53.
3. Friesema ECH, et al. Mechanisms of disease: psychomotor retardation and high T3 levels caused by mutations in monocarboxylate transporter 8 (2006) *Nature Clin Prac* 2: 512-23.

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