MCCC1 and *MCCC2* Gene Analysis in 3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency

Clinical Features:
Isolated 3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency is caused by defects in the mitochondrial 3-MCC enzyme. The phenotype of 3-MCC deficiency is highly variable ranging from severe neurological abnormalities and death in infancy to asymptomatic adults. A severe presentation of 3-MCC deficiency may include a Reye-like illness, ketoacidosis, hypoglycemia, hyperammonemia, psychomotor retardation, seizures, symptoms of cardiorespiratory failure and coma, while a mild presentation can include fatigue and weakness during catabolic episodes or mild developmental delay. Presentations with cardiomyopathy, brain atrophy, and fatty infiltration of liver or muscle may also occur.[1] This disorder is the organic aciduria most frequently detected in tandem mass spectrometry-based newborn screening programs. Often, a child with a positive newborn screen will have follow-up testing consistent with 3-MCC deficiency but never present with symptoms of the disorder. In 36 patients identified by a positive newborn screen result, 69% remained asymptomatic at a follow-up of at least 3 years, while the remainder had clinical findings that included various neurological symptoms and acute metabolic decompensation.[3] However the authors note that the neurological symptoms may have explanations other than 3-MCC deficiency.[3] A positive newborn screen in an infant may also lead to the detection of an asymptomatic mother and siblings.

Inheritance:
Autosomal recessive

Genetics:
The 3-MCC enzyme catalyzes the fourth step of leucine catabolism converting 3-methylcrotonyl-CoA to 3-methylglutaconyl-CoA. 3-MCC is composed of heterodimers of alpha and beta subunits encoded by the *MCCC1* (MCCA) and *MCCC2* (MCCB) genes, respectively. Patients with 3-MCC deficiency have elevated levels of 3-hydroxyisovalerate and 3-methylcrotonylglycine in urine and elevated levels of 3-hydroxyisovalerylcarnitine in blood and urine. These findings are often in combination with severe secondary carnitine deficiency. There does not appear to be an association between the severity of the biochemical phenotype and the clinical phenotype. Patients with clinical features of 3-MCC deficiency typically have fibroblast enzyme activities less than 2% of controls, although some patients may have activities 12% of controls. A number of individuals who were heterozygous for a single variant in the *MCCC1* gene have been reported with a mild biochemical phenotype and residual MCC activity greater than 20% of controls. Approximately half of these individuals had non-specific neurologic features, some of which have been reported in patients with 3-MCC deficiency.[4] The *MCCC1* gene, coding for the alpha-subunit, is on chromosome 3q26-q28 and

has 19 exons and the *MCCC2* gene, coding for the beta-subunit, is on chromosome 5q13 and has 17 exons.

Test Methods:
Variant analysis of the *MCCC1* and *MCCC2* genes is performed on genomic DNA from the submitted specimen. GeneDx offers the option of first testing the *MCCC2* gene via bi-directional sequencing of the entire coding sequence (exons 1-17) and intron/exon boundaries followed by *MCCC1* gene analysis if necessary (sequential testing). Alternatively, both tests can be ordered simultaneously if a more rapid turnaround time is required. If clinically indicated, for patients who have a single variant identified after full sequencing of both the *MCCC1* and *MCCC2* genes, GeneDx will perform reflex deletion/duplication testing (ExonArrayDx) at no additional charge. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
In two separate studies of patients with a biochemically and/or enzymatically confirmed diagnosis of 3-MCC deficiency, two variants were identified in either the *MCCC1* or *MCCC2* gene in 28/28 individuals.[1,2] Approximately 64% of 3-MCC patients had variants in the *MCCC2* gene.[2] In another study, variant analysis of both genes in 83 patients identified two variants in 76 individuals; a single variant was identified in the remaining patients.[3] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:
Variants in *MCCC1* and *MCCC2* occur throughout the gene, without evidence of hotspots. A correlation between genotype and biochemical or clinical phenotype has not been observed.[3] The majority of variants that have been identified in *MCCC1* and *MCCC2* are missense, nonsense, frameshift, small insertions/deletions, and spice site changes. Several exon-level deletions have been described in the *MCCC1* gene, to our knowledge no exon-level deletions have been described in *MCCC2*. Most variants are private.[3] A p.Arg385Ser variant has been identified as a recurrent variant in the *MCCC1* gene, has been shown to have a dominant negative effect and may lead to biochemical and clinical symptoms in heterozygous individuals.[3] This variant does not predict clinical phenotype; however, as it has been described in both severely affected patients and asymptomatic individuals.[3]

References: (12 pt bold)

1. Stadler, SL, et al. (2006) Hum Mutat 27(8):748-759 PMID: 16835865.
2. Dantas, MF, et al. (2005) Hum Mutat 26(2):164 PMID: 16010683.
3. Grunert et al., (2012) Orphanet J Rare Dis 7:31 PMID: 22642865.
4. Morscher RJ et al., (2012) Mol Genet Metab 105:602-606 PMID: 22264772