THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

MEF2C Analysis

Clinical Features:

Mutations of the *MEF2C* gene [OMIM # 600662] have been identified in patients with severe mental retardation, stereotypic movements, hypotonia, and epilepsy (1-4). Patients can also present with facial dysmorphic features and cerebral malformations. Brain imaging is typically abnormal, including nonspecific anomalies of the corpus callosum, enlarged ventricles, periventricular white matter hyperintensities and cortical atrophy (2). Phenotypic overlap exists between patients with *MEF2C* mutations and atypical Rett syndrome (2, 4).

Molecular Genetics:

MEF2C that codes for the Mads Box Transcription Enhancer Factor 2, Polypeptide C, is located at 5q14.3 and contains 10 coding exons. Zweier, *et al*, 2010 detected four de novo mutations in *MEF2C* in 362 patients with severe mental retardation of unknown etiology. Gross deletions of 5q14.3 including partial and whole deletions of *MEF2C* have also been reported (4).

MEF2C belongs to the myocyte enhancer factor 2 (MEF2) subfamily of the MADS (MCM1-agamous-deficiens-serum response factor) gene family of transcription factors. *MEF2C* plays an important role in the development and maintenance of multiple organ systems. The phenotype overlap of *MEF2C* and atypical Rett syndrome is probably due to the involvement of a common pathway (4).

Inheritance:

The frequency of *MEF2C* mutations remains unknown. *MEF2C* mutations are inherited in an autosomal dominant pattern and are typically de-novo. Germline mosaicism has not been reported but remains a possibility.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *MEF2C* 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. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. 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.

MEF2C sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

MEF2C deletion/duplication analysis

Sample specifications:	3 to10 cc 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. Le Meur N, Holder-Espinasse M, Jaillard S et al. MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations. J Med Genet 2010: 47: 22-29.
2. Novara F, Beri S, Giorda R et al. Refining the phenotype associated with MEF2C haploinsufficiency. Clin Genet 2010: 78: 471-477.
3. Nowakowska BA, Obersztyn E, Szymańska K et al. Severe mental retardation, seizures, and hypotonia due to deletions of MEF2C. Am J Med Genet B Neuropsychiatr Genet 2010: 153B: 1042-1051.
4. Zweier M, Gregor A, Zweier C et al. Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression. Hum Mutat 2010: 31: 722-733.

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