THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Wiedemann-Steiner syndrome testing: Mutation analysis of *KMT2A (MLL)*

Clinical Features

Wiedemann-Steiner syndrome [OMIM#605130] is a rare disorder characterized by excessive growth of terminal hair around the elbows (hypertrichosis cubiti), short stature, intellectual disability and characteristic facial features (1). Facial features include long eyelashes, think or arched eyebrows, downslanting and vertically narrow palpebral fissures, broad nasal bridge and wide nasal tip (1).

Molecular Genetics

Jones *et al.* (2012) identified mutations in *KMT2A* (*MLL)* [OMIM#159555] in five out of six patients with clinical features consistent with Wiedemann-Steiner syndrome (1). All mutations were predicted to result in protein truncation. *KMT2A* encodes for a histone methyltransferase that regulates chromatin-mediated transcription.

Inheritance

Wiedemann-Steiner syndrome is an autosomal dominant condition. All mutations identified in *KMT2A* to date have been *de novo*. Recurrence risk for parents in cases with a confirmed *de novo* mutation is <1%.

Test methods

Comprehensive sequence coverage of the coding regions and splice junctions of the *KMT2A* 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. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

KMT2A (MLL) sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1,000
CPT codes:	81406, 81407
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

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. Jones WD, Dafou D, McEntagart M et al. De novo mutations in MLL cause Wiedemann-Steiner syndrome. Am J Hum Genet 2012: 91: 358-364.

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