THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Warburg Micro Syndrome

Clinical Features:

Warburg Micro syndrome [OMIM #600118] is a rare autosomal recessive condition characterized by ocular and neurodevelopmental abnormalities and hypothalamic hypogonadism (1, 2). Key clinical features include microphthalmia, microcornia, congenital cataracts, optic atrophy, microcephaly, cortical dysplasia and atrophy, congenital hypotonia, severe intellectual disability, and spastic diplegia (1, 2). Progressive joint contractures, growth failure, kyphoscoliosis and hypertrichosis have also been described in a proportion of affected individuals (1). In addition to the characteristic ocular findings, common facial features include deep set eyes, wide nasal bridge and a narrow mouth (1). Brain magnetic resonance imaging (MRI) of affected individuals consistently shows polymicrogyria in the frontal and parietal lobes, wide sylvian fissures, thin corpus callosum and increased subdural spaces (1).

Molecular Genetics:

Aligianis *et al*. (2) detected *RAB3GAP1* [OMIM# 602536] mutations in 12 of 18 (67%) families with Warburg Micro syndrome. *RAB3GAP1* encodes the catalytic subunit of the Rab3 GTPase-activating protein, which has a role in exocytosis and is thought to be involved in the regulation of neurotransmitter release and synaptic plasticity in the brain (1). Nonsense, missense, frameshift and splicing mutations have been identified in the *RAB3GAP1* gene (1, 2).

A homozygous splicing mutation in *RAB3GAP2* [OMIM #609275] has been described in a Turkish patient from a consanguineous family (3). Mutations in *RAB3GAP2* have also been described in patients with Martsolf syndrome [OMIM# 212720], which has significant phenotypic overlap with Warburg Micro syndrome. These findings suggest that functionally severe *RAB3GAP2* mutations lead to Warburg Micro syndrome, whereas less severe mutations lead to the milder clinical phenotype of Martsolf syndrome (3, 4). *RAB3GAP2* encodes the non-catalytic subunit of the Rab3 GTPase-activating protein, which is thought to have a key role in neurodevelopment (3, 4).

Bem *et al.* (5) detected *RAB18* [OMIM #602207] mutations in five consanguineous families with Warburg Micro syndrome who had previously had *RAB3GAP1* or *RAB3GAP2* excluded. Further analysis of 58 families with either Warburg Micro or Martsolf syndrome identified *RAB18* mutations in one family with a Warburg Micro syndrome phenotype (5). Missense, small deletions, and anti-termination mutations have been described in the *RAB18* gene (5). Knockout rab18 zebrafish models suggest that *RAB18* has a highly conserved developmental role that could account for the structural abnormalities observed in Warburg Micro syndrome (5).

Liegel *et al*. (6) detected homozygous mutations in *TBC1D20* [OMIM #611663] in 7 individuals from 5 families of varied ethnic origins who had previously undergone negative testing of the *RAB3GAP1*, *RAB3GAP2*, and *RAB18* genes. Individuals with *TBC1D20* mutations are thought to be clinically indistinguishable from those with mutations in the three previously described genes (6). Homozygous loss-of-function mutations in *Tbc1d20* in blind-sterile (*bs*) mice cause male infertility and bilateral lenticular cataracts (6, 7).

Inheritance:

Warburg Micro syndrome is inherited in an autosomal recessive pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel 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.

Warburg Micro syndrome panel (Sequencing and del/dup of *RAB3GAP1, RAB3GAP2, RAB18,* and *TBC1D20*)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2,500
CPT codes:	81406
	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for this panel.
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. Morris-Rosendahl DJ, Segel R, Born AP et al. New RAB3GAP1 mutations in patients with Warburg Micro Syndrome from different ethnic backgrounds and a possible founder effect in the Danish. Eur J Hum Genet 2010: 18: 1100-1106.
2. Aligianis IA, Johnson CA, Gissen P et al. Mutations of the catalytic subunit of RAB3GAP cause Warburg Micro syndrome. Nat Genet 2005: 37: 221-223.
3. Borck G, Wunram H, Steiert A et al. A homozygous RAB3GAP2 mutation causes Warburg Micro syndrome. Hum Genet 2011: 129: 45-50.
4. Aligianis IA, Morgan NV, Mione M et al. Mutation in Rab3 GTPase-activating protein (RAB3GAP) noncatalytic subunit in a kindred with Martsolf syndrome. Am J Hum Genet 2006: 78: 702-707.
5. Bem D, Yoshimura S, Nunes-Bastos R et al. Loss-of-function mutations in RAB18 cause Warburg micro syndrome. Am J Hum Genet 2011: 88: 499-507.
6. Liegel RP, Handley MT, Ronchetti A et al. Loss-of-function mutations in TBC1D20 cause cataracts and male infertility in blind sterile mice and Warburg micro syndrome in humans. Am J Hum Genet 2013: 93: 1001-1014.
7. Varnum DS. Blind-sterile: a new mutation on chromosome 2 of the house mouse. J Hered 1983: 74: 206-207.

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