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 novel and/or potentially 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.

**Warburg Micro syndrome Sequencing panel (RAB3GAP1, RAB3GAP2, RAB18, and TBC1D20 sequencing)**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $3,400
- **CPT codes:** 81407
- **Turn-around time:** 8 weeks

*Note: We cannot bill insurance for this panel.*

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

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $1,545
- **CPT codes:** 81407
- **Turn-around time:** 4 - 6 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.

**References:**