



Rhabdoid Tumor Predisposition Syndrome Testing: Mutation analysis of *SMARCA4*

Clinical Features:

Rhabdoid tumor predisposition syndrome (RTPS) [OMIM #603254] is characterized by an increased risk of rhabdoid tumors. Rhabdoid tumors are aggressive embryonal neoplasms that most commonly develop in early infancy or childhood (1). Central nervous system rhabdoid tumors are typically referred to as atypical teratoid/rhabdoid tumors (AT/RT), and extracranial rhabdoid tumors (which commonly occur in the kidneys) are typically referred to as malignant rhabdoid tumors (MRT) (2). Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) has recently been reclassified by Foulkes *et al.* (2014) as a type of rhabdoid tumor, and is also now referred to as malignant rhabdoid tumor of the ovary (2). SCCOHT typically develops in childhood or early adulthood, with a mean age of diagnosis in the general population of 23 years (3). Rhabdoid tumors typically carry a poor prognosis and are often fatal (2).

Molecular Genetics:

Schneppenheim *et al* (2010) described a family with two siblings with rhabdoid tumors with a *SMARCA4* mutation (1). The mutation was inherited from their unaffected father, suggesting incomplete penetrance. Witkowski *et al* (2014) identified germline heterozygous mutations in *SMARCA4* in four unrelated families with multiple cases of SCCOHT (3). Tumor testing in these families revealed somatic loss of the second *SMARCA4* allele, consistent with *SMARCA4* acting as a tumor suppressor gene (3). Heterozygous mutations in *SMARCA4* are also associated with Coffin Siris syndrome (4). Truncating mutations in the *SMARCA4* gene typically lead to RTPS, whereas missense mutations are typically associated with Coffin Siris.

Inheritance:

Mutations in *SMARCA4* are inherited in an autosomal dominant manner, and may be inherited or occur *de novo*. Recurrence risk for unaffected parents of an isolated case may be up to 50%, due to incomplete penetrance.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SMARCA4* gene is performed. Comprehensive sequence coverage of the coding regions and splice junctions of this 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.

[SMARCA4 sequencing and deletion/duplication analysis](#)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1700
CPT codes:	81406, 81407
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 or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Schneppenheim R, Frühwald MC, Gesk S et al. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. *Am J Hum Genet* 2010; 86: 279-284.
2. Foulkes WD, Clarke BA, Hasselblatt M et al. No small surprise - small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour. *J Pathol* 2014; 233: 209-214.
3. Witkowski L, Carrot-Zhang J, Albrecht S et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcaemic type. *Nat Genet* 2014; 46: 438-443.
4. Tsurusaki Y, Okamoto N, Ohashi H et al. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat Genet* 2012; 44: 376-378.

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