Hereditary Renal Cancer Panel

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Pathogenic germline variants in multiple genes have been implicated in hereditary renal cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or related cancers in a single individual or in a closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including nonrenal cancers. See Genes Tested table below for more details regarding the genes and syndromes included on the Hereditary Renal Cancer Panel. Genes included on this panel are also included in other ARUP hereditary cancer tests. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table.

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication 2010214

Method: Massively Parallel Sequencing / Sequencing / Multiplex Ligation-Dependent Probe Amplification (MLPA)

- Use to confirm a diagnosis of a hereditary renal cancer syndrome in individuals with a personal or family history of renal cancer
- Testing minors for adult-onset conditions is not recommended and will not be performed on minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Genes

See the Genes Tested table for genes included in the panel.

Etiology

Approximately 3-5% of renal cancers are associated with a hereditary cause.[1]

Inheritance

- All genes tested on the hereditary renal cancer panel are autosomal dominant with the exception of the *SDHD* gene, which is autosomal dominant with paternal parent-of-origin effect.
- Some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.
- See the Genes Tested table for additional details.

Test Interpretation

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy as sensitivity for mosaic variants is low with methodology used for germline assays
- Individuals with hematological malignancy and/or a previous allogeneic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.

- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Long-range PCR followed by nested Sanger sequencing is performed on the following gene and exons:
  - *PMS2* (NM_000535) 11, 12, 13, 14, 15
- Bidirectional Sanger sequencing is performed on the following genes and exons:
  - *MSH2* (NM_000251) 5
  - *PMS2* (NM_000535) 7
  - *PTEN* (NM_000314) 9
- Multiplex ligation-dependent probe amplification (MLPA) is performed on the following gene to call exon-level deletions and duplications:
  - *PMS2* (NM_000535)

Clinical Sensitivity

Variable, dependent on phenotype/condition

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9
Exon-level deletions/duplications (MLPA)	>99	>99

[a] PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

[b] Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c] In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- Deletions/duplications within *PMS2* exons 12-15 may not be distinguishable from the *PMS2CL* pseudogene and may be reported as inconclusive.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Sequence variants in *EPCAM*
  - The following exons are not sequenced due to technical limitations of the assay:
    - *FLCN* (NM_001353229) 7
    - *SDHA* (NM_004168) 14; (NM_001294332) 13; (NM_001330758) 12
    - *SDHC* (NM_001035511) partial exon 5 (Chr1:161332225-161332330); (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
    - *SDHD* (NM_001276506) 4
    - *VHL* (NM_001354723) 2
- The following may not be detected:

- Deletions/duplications/insertions of any size by MPS
- Large duplications less than 3 exons in size
- Noncoding transcripts
- Single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement
- Some variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
- Low-level somatic variants
- Deletions/duplications in the following exons:
  - *FLCN* (NM_001353229) 7
  - *PTEN* (NM_000314, NM_001304718) 9; (NM_001304717) 1,10
  - *SDHA* (NM_004168) 1,10-15; (NM_001294332) 1,9-14; (NM_001330758) 1,10-13
  - *SDHD* (NM_001276506) 4
  - *VHL* (NM_001354723) 2

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
BAP1	603089	BAP1-TPDS BAP1-inactivated melanocytic tumors, basal cell carcinoma, cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, uveal melanoma	AD
DICER1	606241	*DICER1*-related disorders CNS, cystic nephroma, ovarian sex cord-stromal tumors, pleuropulmonary blastoma, thyroid	AD
EPCAM (Exon 9 deletions/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
FH	136850	FH tumor predisposition syndrome/HLRCC Cutaneous and uterine leiomyomata, papillary type 2 renal cancer, paraganglioma, pheochromocytoma	AD
		Fumarase deficiency	AR
FLCN	607273	BHDS Fibrofolliculomas, pulmonary cysts/history of pneumothorax, renal cancer	AD
MET	164860	HPRCC Papillary type 1 renal cancer	AD
MLH1	120436	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH2	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
MSH6	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma, renal cell carcinoma, thyroid, and others	AD
SDHA	600857	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHB	185470	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHC	602413	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD
SDHD	602690	HPP syndromes GIST, paraganglioma, pheochromocytoma, pulmonary chondroma, renal clear cell carcinoma	AD[a]
SMARCA4	603254	Rhabdoid tumor predisposition syndrome Associated cancer(s)/tumor(s): rhabdoid tumor	AD
SMARCB1	601607	Rhabdoid tumor predisposition syndrome Associated cancer(s)/tumor(s): rhabdoid tumor	AD
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD
TSC1	605284	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD
TSC2	191092	TSC Cardiac rhabdomyoma, fibromas, renal angiomyolipoma, retinal and other hamartomas, SEGA, and others	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
VHL	608537	VHL syndrome Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, retinal angioma	AD

[a] Paternal parent-of-origin effect.

AD, autosomal dominant; AR, autosomal recessive; BAP1-TPDS, BAP1 tumor predisposition syndrome; BHDS, Birt-Hogg-Dube syndrome; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell cancer; HNPCC, hereditary nonpolyposis colorectal cancer; HPP, hereditary paraganglioma-pheochromocytoma; HPRCC, hereditary papillary renal cell carcinoma; LFS, Li-Fraumeni syndrome; RTPS, rhabdoid tumor predisposition syndrome; SCCOHT, small-cell carcinoma of the ovary, hypercalcemic type; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau

References

1. Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. *Adv Chronic Kidney Dis*. 2014;21(1):81-90.

Related Information

Hereditary Cancer Germline Genetic Testing