Hereditary Central Nervous System Cancer Panel, Sequencing and Deletion/Duplication

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Pathogenic germline variants in multiple genes have been implicated in hereditary central nervous system (CNS) tumors and cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50), the presence of any number of CNS tumors in a single individual or closely related family member(s), and variable systemic manifestations. See the Genes Tested table for more details regarding the genes included on this test and associated cancers and syndromes.

Featured ARUP Testing

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

Hereditary Central Nervous System Cancer Panel, Sequencing and Deletion/Duplication 3001633

Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-dependent Probe Amplification

- Recommended test to confirm a hereditary cause of CNS cancer in individuals with a personal or family history of CNS cancer
- Testing minors for adult-onset conditions is not recommended; testing will not be performed in minors without prior approval.
- For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

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

Refer to the Genes Tested table for genes included in the panel.

Etiology

Approximately 5% of CNS tumors are associated with a hereditary cause.

Inheritance

- Autosomal dominant
- Some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

Test Interpretation

Contraindications for Ordering

- For individuals with a suspected diagnosis of Lynch syndrome, consider testing specific to Lynch syndrome as some relevant variants are not included on this panel. Refer to Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC) for more information.
- Should not be ordered to detect somatic variants associated with malignancy because 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 polymerase chain reaction (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)

Sensitivity/Specificity

Clinical Sensitivity

Variable, dependent on phenotype

Analytic Sensitivity/Specificity

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

Limitations

- A negative result does not exclude a heritable form of CNS cancer or other cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient 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 targeted gene(s)
  - Regulatory region 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:
  - *APC* (NM_001354896) exon 12
  - *APC* (NM_001354898, NM_001354904) exon 2
  - *APC* (NM_001354900) exon 11
  - *MEN1* (NM_001370251) exon 8
  - *VHL* (NM_001354723) exon 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.
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - Deletions/duplications in the following exons:
    - *APC* (NM_001354896) 12
    - *APC* (NM_001354898, NM_001354904) 2
    - *APC* (NM_001354900) 11
    - *MEN1* (NM_001370251) 8
    - *PTEN* (NM_000314, NM_001304718) 9
    - *PTEN* (NM_001304717) 1,10
    - *RB1* (NM_000321) 22
    - *SMARCE1* (NM_003079) 7,10-11
    - *VHL* (NM_001354723) 2
  - The following regions may have reduced sequencing sensitivity due to technical limitations of the assay:
    - *RB1* (NM_000321) exon 22
    - *SUFU* (NM_016169, NM_001178133) exon 1

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
ALK	105590	*ALK*-related neuroblastic tumor susceptibility Ganglioneuroblastoma, ganglioneuroma, neuroblastoma	AD
APC	611731	FAP AFAP GAPPS Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreatic, thyroid, and others	AD
DICER1	606241	*DICER1*-related disorders Pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
EPCAM (Exon 9 deletion/duplications only)	185535	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreatic, prostate, renal pelvis and/or ureter, stomach, and others	AD
HRAS	190020	Costello syndrome Neuroblastoma, rhabdomyosarcoma, transitional cell carcinoma of the bladder	AD
LZTR1	600574	Schwannomatosis	AD
		Noonan syndrome	AR
MEN1	613733	MEN type 1 Adrenocortical, carcinoid, gastro-entero-pancreatic (GEP) neuroendocrine tumors, meningioma, parathyroid, pituitary, thyroid	AD
MLH1	120436	Lynch syndrome/HNPCC	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
		Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	
		CMMRD	AR
MSH2	609309	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
MSH6	600678	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
NF1	613113	NF1 Breast, GIST, gliomas, leukemia, malignant peripheral nerve sheath tumors, neurofibromas, pheochromocytoma	AD
NF2	607379	NF2 Astrocytoma, ependymoma, meningioma, schwannoma	AD
PMS2	600259	Lynch syndrome/HNPCC Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others	AD
		CMMRD	AR
POT1	606478	*POT1* tumor predisposition syndrome Angiosarcoma, chronic lymphocytic leukemia, cutaneous melanoma, glioma	AD
PRKAR1A	188830	Carney complex Endocrine tumor or overactivity, myxoma, schwannoma	AD
PTCH1	601309	NBCCS/Gorlin syndrome Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	AD
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma,[a] renal cell carcinoma, thyroid, and others	AD
RB1	614041	Hereditary retinoblastoma Melanoma,[a] osteosarcoma, pinealoblastoma, retinoblastoma, retinoma, soft tissue sarcoma	AD
SMARCA4	603254	Coffin-Siris syndrome, RTPS Rhabdoid tumors located in CNS, kidney, ovary (SCCOHT), and others	AD
SMARCB1	601607	Coffin-Siris syndrome, RTPS Rhabdoid tumors located in CNS, kidney, and others; schwannomatosis	AD
SMARCE1	603111	Coffin-Siris syndrome Meningioma	AD

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
SUFU	607035	NBCCS/Gorlin syndrome Basal cell carcinoma, cardiac and ovarian fibromas, medulloblastoma	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
VHL	608537	VHL syndrome Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, retinal angioma	AD

[a]Association is suggested but not well-established at this time.

AD, autosomal dominant; AFAP, attenuated FAP; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis colorectal cancer; LFS, Li-Fraumeni syndrome; MEN, multiple endocrine neoplasia; NBCCS, nevoid basal cell carcinoma syndrome; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; 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

Related Information

Primary Brain Tumors – Brain Tumor Molecular Markers

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