Weill Cornell Medicine
Clinical Genomics Lab

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# Whole Exome Sequencing Test for Cancer - EXaCT-1

## CLINICAL INFORMATION

Patient information

**Name:** CLINICAL GENOMICS LAB
**MRN:** 00000084
**Sex:** U
**DOB:** 19XX-01-01

Physician information

**Referring:** ROHAN RAMAKRISHNA

Specimen information

| | Case | Control |
|---|---|---|
| **IDs:** | S18-XXXXX;B3 | GX19-X1;P2;NYH+B |
| **Type:** | FFPE | Blood |
| **Collected:** | 2019-01-23 | 2019-01-08 |
| **Received:** | 2019-01-23 | 2019-01-08 |

Report information

**Signing pathologist:** Wei Song, MD, PhD
**Report type:** Original/Final

Tumor information

**Tumor type:** Astrocytoma, NOS
**Primary site:** Brain
**Tissue tested:** Brain
**Neoplastic content:** 87.0%

# Results

## GENOMIC ALTERATIONS:

### Summary

**Somatic alterations in clinically relevant genes**

A set of 65 clinically relevant genes was investigated. 1 alteration was found in these genes (listed below).

**Other somatic alterations in cancer genes**

A set of 572 known cancer genes was investigated. 28 alterations in these cancer associated genes were found (listed below).

**Somatic alterations of unknown significance**

17 gene(s) with point mutations or indels and 10 copy number alteration(s) were found (listed below).

## Clinically relevant genomic alterations

These alterations occur in genes that are deemed clinically relevant because: they are targets of drugs, they confer resistance or susceptibility to treatment, or for other clinically relevant reasons (see Appendix).

**Somatic mutations and indels**

| Gene name (coordinates) | Variant | Interpretation |
|---|---|---|
| IDH1<br>2:209,113,112 | p.Arg132His (c.395G>A)<br>Depth: 151 (108)<br>VAF: 54.3% | IDH1 or IDH2 mutations are found in >70% of lower grade diffusely infiltrative gliomas and in >90% of secondary glioblastoma. IDH mutational status has been reported to be a favorable prognostic indicator relative to wild-type gliomas of similar histology, regardless of grade. Therapeutic strategies exploiting mutated IDH protein, including through direct inhibition and vaccine-based approaches, are currently the subject of preclinical research and clinical trials. |

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Depth: tumor read depth (normal read depth); VAF: tumor variant allele frequency

# Other genomic alterations in cancer genes

These alterations occur in genes that are cancer associated (see Appendix).

### Somatic mutations and indels

| Gene name (coordinates) | Classification | Tumor (normal) read depth | Tumor VAF | Protein change / Notes |
|---|---|---|---|---|
| TP53 17:7,577,153 | missense | 54 (73) | 77.8% | p.Gly262Val (c.785G>T) |
| ATRX X:76,890,149 | frameshift | 42 (85) | 50.0% | p.Thr1582Lysfs*24 (c.4745delC) |

AA: amino-acid; VAF: variant allele frequency; Genomic coordinates are based on human reference GRC37/hg19 and are 1-based. Alleles are based on the positive strand of the human reference genome. Alterations with VAF < 10%, coverage < 30x or < 5 mutated reads are below optimal detection conditions and should be considered as putative.

### Copy number alterations

| Altered Region (location) | Classification of SCNA | Number of cancer genes | Cancer genes |
|---|---|---|---|
| 3:96,533,658-121,265,340 | focal loss | 2 | TFG CBLB |
| 3:121,659,281-155,205,854 | focal loss | 6 | GATA2 RPN1 CNBP FOXL2 ATR WWTR1 |
| 3:155,520,348-155,621,698 | focal loss | 1 | GMPS |
| 3:167,077,710-171,574,472 | focal loss | 1 | MECOM |
| 6:203,540-8,102,709 | focal loss | 1 | IRF4 |
| 6:93,953,199-107,955,692 | focal loss | 1 | PRDM1 |
| 6:138,413,290-139,694,673 | focal loss | 1 | ECT2L |
| 6:166,952,212-170,893,526 | focal loss | 2 | FGFR1OP MLLT4 |
| 16:15,489,908-24,043,510 | focal loss | 2 | MYH11 PALB2 |
| 19:42,584,152-55,179,395 | focal loss | 9 | CIC BCL3 CBLC ERCC2 KLK2 PPP2R1A ZNF331 TFPT CNOT3 |

Genomic coordinates are based on human reference GRC37/hg19. See Appendix for all definitions.

# Genomic alterations of unknown significance

These alterations are not known to have any effect on the disease, but are here reported in the event that in the future progress in scientific knowledge could determine their role (see Appendix).

### Somatic mutations and indels

| Gene name (coordinates) | Classification | Tumor (normal) read depth | Tumor VAF | Protein change / Notes |
|---|---|---|---|---|
| LRRC40 1:70,641,509 | missense | 97 (52) | 36.1% | p.Asn321Asp (c.961A>G) |
| KIAA1715 2:176,829,121 | nonsense | 122 (87) | 48.4% | p.Val158* (c.472delG) |
| TOPAZ1 3:44,285,908 | missense | 252 (177) | 42.9% | p.Thr637Met (c.1910C>T) |

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**Patient Name:** CLINICAL GENOMICS LAB **EXaCT-1 Report** **Report date:** 2019-02-22

| Gene name (coordinates) | Classification | Tumor (normal) read depth | Tumor VAF | Protein change / Notes |
|---|---|---|---|---|
| RABL6 9:139,732,389 | missense | 205 (126) | 55.6% | p.Arg402His (c.1205G>A) |
| KRTAP5-5 11:1,651,120 | missense | 15 (18) | 46.7% | p.Arg17Leu (c.50G>T) |
| NELL1 11:21,594,917 | missense | 23 (39) | 39.1% | p.Thr782Ala (c.2344A>G) |
| KRT6A 12:52,881,881 | missense | 64 (59) | 35.9% | p.Asn477Lys (c.1431T>A) |
| SOAT2 12:53,497,414 | missense | 202 (196) | 39.6% | p.Gly18Glu (c.53G>A) |
| NCOR2 12:124,911,204 | missense | 170 (114) | 44.7% | p.Met431Thr (c.1292T>C) |
| MTUS2 13:29,933,533 | missense | 143 (116) | 39.9% | p.Val1024Ile (c.3070G>A) |
| CCDC144NL 17:20,769,995 | missense | 227 (54) | 44.9% | p.Gly146Glu (c.437G>A) |
| CCDC144NL 17:20,770,002 | missense | 227 (54) | 44.9% | p.Ala144Ser (c.430G>T) |
| CCDC144NL 17:20,770,003 | missense | 226 (54) | 45.1% | p.Gln143His (c.429G>C) |
| FTHL17 X:31,089,692 | missense | 100 (112) | 39.0% | p.Asp127Asn (c.379G>A) |
| EDA X:69,247,758 | missense | 17 (48) | 47.1% | p.Pro193Leu (c.578C>T) |
| DOCK11 X:117,810,663 | missense | 83 (82) | 38.6% | p.Gly1808Val (c.5423G>T) |
| F8 X:154,215,532 | missense | 281 (182) | 42.3% | p.Leu217His (c.650T>A) |

AA: amino-acid; VAF: variant allele frequency; Genomic coordinates are based on human reference GRC37/hg19 and are 1-based. Alleles are based on the positive strand of the human reference genome. Alterations with VAF < 10%, coverage < 30x or < 5 mutated reads are below optimal detection conditions and should be considered as putative.

## Copy number alterations

| Altered Region (location) | Classification of SCNA | Number of genes | Selected genes of unknown significance (if any) |
|---|---|---|---|
| None reported. | | | |

Genomic coordinates are based on human reference GRC37/hg19. See Appendix for all definitions.

**Electronically signed by:** Wei Song, MD, PhD, **on** 2019-02-22 at 16:11:59

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## Method

Genomic DNA was extracted from macrodissected formalin-fixed paraffin-embedded (FFPE) tumor, or cored frozen, OCT-embedded tumor and peripheral blood lymphocytes of the patient's specimens using the Promega Maxwell 16 MDx. Estimation of tumor content is based on the analysis of the sequencing data using CLONET version 1.0 [1]. Sequencing was performed using INS100 HiSeq 2500. A total of 21,522 genes were analyzed with an average coverage of 110.0 reads (98.0) using HALOPLEX. 82,759,256 (79,409,073) short reads were aligned to GRCh37reference using BWA [2] and processed accordingly to EXaCT-1 pipeline (v1.0.00). The capture efficiency was 8983.0% (8191.0%).

**NB:** numbers in parentheses refer to the corresponding patient's control sample.

1. Prandi D. et al. Unraveling the clonal hierarchy of somatic genomic aberrations. Genome Biol 2014;15:439. doi:10.1186/s13059-014-0439-6.
2. Li, Heng, and Durbin Richard. Fast and Accurate Long-read Alignment with Burrows-Wheeler Transform. Bioinformatics 2010;26(5)(March 1):589–595. doi:10.1093/bioinformatics/btp698

## Limitations of the assay

1. The analytical sensitivity of the assay is approximately 10% (with a minimum neoplastic content of 20%), thus, mutations present in a lower percentage of cells may not be identified by this assay. Use of insufficient DNA template can result in low PCR product yields, and sequence signals may fall below detection limits.
2. The human exome is not captured in its entirety, because not all human genes are identified and some genes may not be amendable to capture. Pathogenic mutations located in genes that are non-coding, have corresponding pseudogenes, contain repetitive or high GC-region will not be detected. Information about low coverage regions by this test is provided on our website at: https://profiler17.med.cornell.edu/supplemental_data/IPMWES/HaloPlex_low_coverage_region.xlsx
3. Medium to large indels above 30% of the read length (>60bp) may not be detected due to the short (~200 bp) Illumina reads.
4. The ability of this assay to identify copy number alterations is reduced in cases with low tumor percentage (e.g., less than 50% tumor); in such cases, copy number alteration data (including the apparent absence of copy number alterations) should be interpreted with caution since the findings may not be representative.
5. Some regions of genes cannot be fully evaluated for mutations or indels because of lack of sufficient coverage due to technical or biological (e.g. copy number loss) aspects.

## Disclaimer

EXaCT-1 was developed and its performance characteristics was determined by the Englander Institute for Precision Medicine/New York Hospital Laboratories. EGFR (exon 19, 20), KRAS (exon 2), BRAF (exon 15), ERBB2 (amplification) and JAK2 (exon 12) have been validated according to NYS/DOH recommendation. All variants from other genes are for investigational use only. This method has not been cleared by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. EXaCT-1 may be used for clinical purpose and should not be regarded as experimental or research only.

The lack of a given genetic alteration in this report does not necessarily indicate the absence of the alteration in the tumor since technical aspects of the assay, including inadequate coverage of some genes, limit the data that can be acquired in some genetic regions.

Alterations that occur in the germline are not reported. If a possible pathogenic germline mutation (inherited) is suspected, then counseling by a board certified genetic counselor will be recommended in note.

## Appendix

**Clinically relevant genes:** These genes are deemed clinically relevant because: they are targets of drugs, they confer resistance or susceptibility to treatment, or for other clinically relevant reasons. As the scientific knowledge increases, this list will be updated accordingly. A total of 1 alterations in 65 genes are considered in this report.

**Somatic alterations of unknown significance in cancer genes or in other genes:** These genes may not be related to the disease. Current scientific knowledge cannot determine the impact of these alterations on the disease. These genes are included herein in the event they become clinically relevant as our knowledge increases. Specifically, this report considers a total of 572 cancer genes that are listed in the section 'Other genomic alterations in cancer genes' if alterations are found.

**Alterations are not listed in ranked order:** The order of the alterations reported as clinically relevant or of unknown significance is **not** associated with predicted effect on tumor development, progression, or resistance to treatment.

**Copy number alterations:** These alterations involve duplication or loss of genomic material. The following definitions are used:

. *Focal* : A genomic alteration in a region involving less than 50 genes.
. *Broad* : A genomic alteration in a region involving 50 genes or more.
. *Copy Number Gain* : A genomic alteration leading to increased copies in tumor relative to the control sample (log2 ratio between 0.5 and 1.0).
. *Copy Number Loss* : A genomic alteration leading to decreased copies in tumor relative to the control sample (log2 ratio between -0.5 and -1.0).
. *Amplification* : Focal, high copy number gain (log2 ratio >= 1.0).
. *Deletion* : Extensive copy number loss, likely corresponding to homozygous deletions (log2 ratio <= -1.0)

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. *Partial* : A genomic alteration affecting part of a gene.
. Note that all genomic coordinates are based on human reference GRC37/hg19.

**Treatment decisions:** The treating physician is responsible to select the most appropriate course of treatment. Decision making about therapy should not be based solely on the information contained in this report.

The report was generated at 2019-02-22T16:11:59.908-05:00; based on version v1.6-66-g13fe96e of software IPM-reportGenerator, on version GRCh37-20170401-201902171800.iks of the IPM knowledge base and cancer genes census, and on version 05ee17a of the results.