Project
Analysis and annotations of BRAF deletions in samples from 20-2047

Requester
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FMI Identifier
DBI_20220221_D.1

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Overview:
This query investigates BRAF deletions in study 20-2047 (FoundationOneLiquidDx-BPA-RET-20-2047). Samples identified with BRAF deletion rearrangements are provided as well as the qualifying BRAF deletion rearrangements. An arcplot is provided for the visualization of rearrangements found.

We analyzed six samples and found 14 different BRAF deletion rearrangements. The most common breakpoint was in intron 10, followed by breakpoints in introns 1, 3, and 8. The most common rearrangement product was exons 1-3 joined to exons 11-18.

The same criteria established to identify BRAF rearrangements in DBI_20210301_A.1 and subsequent follow-ups was used in this query, see **Definitions**.

Specifics:
- **Datafreeze:** Feb 2022
- **Study:** 20-2047 (mo29112)
- **Disease(s):** Colorectal, cancer of unknown primary
- **Baitset(s):** AB1
- **Genes:** BRAF

Definitions

BRAF Deletion	Rearrangements affecting BRAF that satisfied the following criteria: - Both rearrangement breakpoints located within BRAF. - Rearrangement is in-strand. In other words, the 5' and 3' product are in the same transcriptional direction in the final rearrangement.

	- Rearrangement is not definitively out of frame.

Caveats:

Notes for comparison to Advanced Genomic Analysis:

Variants included in this data are delivered from the research dataset. Therefore, they may differ from the standard and advance genomic analyses and may have differences due to distinct filters that are applied to the research dataset.

Notes for LBx Threshold:

For liquid biopsy queries, our recommended benchmark is to examine samples meeting the following criteria:

- Samples with cTF >= 1%, and
- Samples with a QC status of "_pass" (excludes "qualified" samples).

We have included two sets of analyses (1) covering all queried specimens and (2) limited only to specimens that meet the LBx Threshold (tabs with *"LBx Threshold" or "LBxT"*).

Visualizations:

Notes for arc plots

1 arc plot was provided for BRAF deletions.

- The x-axis depicts approximate position along the BRAF transcript. Exons are drawn to scale, but introns are not.
- Arcs are drawn connecting two breakpoints to represent the portion of the gene that is deleted. Orange arcs appearing below the exon/intron graph represent known/likely deletions.
- The width of arcs represents the frequency of that combination of breakpoints, so a thicker line indicates that combination is more common.
- The height of the lollipops indicates the total number of breaks that occur in the intron or exon of interest

Data Description:

Variants Tab: detailed summary of variants

trf	Unique permanent sample identifier.
bait_set	Baitsets (e.g. T7, DX1) included in query: **'DX1':** *FoundationOneCDx* testing, all solid tumors (samples from FFPE tissue biopsies). **'T7':** *FoundationOne* testing, all solid tumors (samples primarily from FFPE tissue biopsies). **'T5a':** Older *FoundationOne* testing, all solid tumors (samples primarily from FFPE tissue biopsies).

	'D2': *FoundationOneHeme* testing, hematopoietic malignancies and sarcomas, and occasionally a non-sarcoma solid tumor (samples primarily from FFPE, peripheral whole blood, and bone marrow aspirate). Includes samples with and without the RNA component. See **rna_qc_status** for details on the RNA portion of the test. **'AB1':** *FoundationOne Liquid CDx testing*, improved circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples). **'CF3':** *FoundationOne Liquid* testing, improved circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples). **'CF2':** *FoundationACT* testing, FMI's initial circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples).
gene	Gene in which alteration was found.
partner_gene	Partner gene for rearrangement events.
pos1_RE	RE events only; genomic coordinates (hg19) of sequencing reads from one partner involved in a rearrangement event. Note that pos1 and pos2 do not depict orientation.
pos2_RE	RE events only; genomic coordinates (hg19) of sequencing reads from the second partner involved in a rearrangement event. Note that pos1 and pos2 do not depict orientation.
alteration_type	SV=short variant/indel, CN=copy number alteration (focal amplification or deletion), RE=rearrangement, NH = nonhuman (viral).
var_status	known/likely=identical or similar alterations that have been reported in cancer, unknown=variants of unknown significance/alterations that have not been reported in cancer; in some cases, unknown copy number alterations can also indicate non-focal events.
coding_type	The coding type of an alteration, specifically: For SVs: ***'missense', 'nonsense', 'nonframeshift', 'frameshift', 'promoter', 'splice', 'nonstart', 'nonstop',*** and ***'synonymous'*** mutations. For CNs: ***'amplification'*** and ***'deletion'*** events. For REs: ***'deletion', 'truncation',*** and ***'rearrangement'*** events. For NHs: ***'non-human'.***

	This is used to determine type displayed on tileplot visualizations.
LBx_threshold	TRUE/FALSE. Flag indicating that the variant's specimen met both our recommended benchmarks for liquid biopsies (LBx). Specifically: Specimen cTF ≥ 1% and had an overall sample QC status of "_pass".
InStrand	TRUE/FALSE. Flag indicating that the resulting rearrangement brings the 5' and 3' product together in the same transcriptional direction
InFrame	Yes/unknown/no. Flag indicating that the rearrangement results in a transcript product that is in-frame
5' Breakpoint	5' most breakpoint of the rearrangement
3' Breakpoint	3' most breakpoint of the rearrangement
5' Product	Translated exons of the 5' end of the rearrangement
3' Product	Translated exons of the 3' end of the rearrangement
5' Transcript	Transcript name for the 5' gene product
3' Transcript	Transcript name for the 3' gene product

Samples Tab: summary of sample characteristic

trf	Unique permanent sample identifier.
msi_status	Microsatellite instability classification based either principal component analysis (PCA) (all non-AB1 baitsets) or on the fraction of unstable repetitive loci across approximately 2000 assayed (AB1), with the following possible outcomes: **'MSI-H':** Positive (MSI-High). Sample has >0.5% unstable loci. **'MSS':** Negative (microsatellite stable). **'MSI ambiguous':** Ambiguous: msi_pc1 score is in-between MSI-H and MSS. **'MSI unknown':** Unknown: Median coverage is below 250X or MSI score is unreliable.
bait_set	Baitsets (e.g. T7, DX1) included in query: **'DX1':** *FoundationOneCDx* testing, all solid tumors (samples from FFPE tissue biopsies). **'T7':** *FoundationOne* testing, all solid tumors (samples primarily from FFPE tissue biopsies). **'T5a':** Older *FoundationOne* testing, all solid tumors (samples primarily from FFPE tissue biopsies).

	'D2': *FoundationOneHeme* testing, hematopoietic malignancies and sarcomas, and occasionally a non-sarcoma solid tumor (samples primarily from FFPE, peripheral whole blood, and bone marrow aspirate). Includes samples with and without the RNA component. See **rna_qc_status** for details on the RNA portion of the test. **'AB1':** *FoundationOne Liquid CDx testing*, improved circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples). **'CF3':** *FoundationOne Liquid* testing, improved circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples). **'CF2':** *FoundationACT* testing, FMI's initial circulating tumor DNA (ctDNA) testing for all solid tumors (using peripheral whole blood samples).
bTMB	An estimation of blood tumor mutational burden (bTMB) using an internal algorithm based on filtered VUS events (Woodhouse et al, PLOS One 2020). bTMB is provided for samples run on FoundationOne Liquid CDx.
rearrangements	Fusions, translocations, and large deletion events, including events that truncate tumor suppressor genes. Comma-separated list, each RE in the format: *Gene1:Gene2* (N/A indicates an intergenic region).
sample_qc_status	Specimen overall QC status.
cTF	Sample estimated cTF, for liquid samples only.
LBx_threshold	TRUE/FALSE. Flag indicating that the sample met both our recommended benchmarks for liquid biopsies (LBx). Specifically: Specimen cTF ≥ 1% and overall sample QC status is "_pass".