

Accession: V12345

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Received: 10/15/21 Reported: 10/25/21



Pet:

Owner:

Species:

Breed:

Sex:

Age:

Site:

Canine

Boxer

Male

7yrs

Left prescap
region

Diagnosis:

High grade mast cell tumor

SearchLight DNA Overview

Biomarkers Identified: 2

KIT

TP53

Number of Clinical Trials:

- This Cancer Type: 1
- General Cancer: 15



2 Diagnostic Biomarkers



2 Prognostic Biomarkers

4 Matching Drugs: Axitinib, Imatinib,
Trametinib, Toseranib

Sample QC Metrics

Specimen Type: FNA Slides

Tumor Content (>20%): Sufficient

Mean Target Coverage (>200x): 405x

SearchLight DNA Summary

This test evaluated 120 cancer genes in the patient's tumor sample. The ABCB1-1Δ (MDR1-1Δ) mutation was not detected, supporting that patient is unlikely to experience ABCB1-1Δ-related adverse effects of chemotherapy. 2 alterations were identified of potential clinical significance for cancer diagnosis, prognosis or treatment.

Integrated review of the genomic data and clinical history as well as pathology reports for patient's lesion supports the diagnosis of mast cell tumor. Specifically, the occurrence of a KIT Internal Tandem Duplication (ITD), as seen in this sample, is common in high grade canine mast cell tumors. In addition, TP53 loss-of-function mutations are also frequently observed in canine mast cell tumors.

SearchLight DNA™ Clinician Report



Therapeutic Biomarkers

Treatment Options Based on Mutations

Drug	Mutation	Available for dogs	Used in humans
Toceranib	KIT Internal Tandem Duplication	Yes ^C	-----
Axitinib	KIT Internal Tandem Duplication	-----	Yes ^A
Imatinib	KIT Internal Tandem Duplication	Yes ^A	Yes ^A

Drug Resistance-Associated Biomarkers

Drug	Mutation
Trametinib	TP53 p.Arg248*

Pharmacogenomic Biomarkers

Gene	Mutation
ABCB1	No mutation



Diagnostic Biomarkers

Described in:

Gene	Mutation	Canine cancer	Human cancer
KIT	Internal Tandem Duplication	Mast Cell Tumor ^B	-----
TP53	p.Arg248*	-----	Yes ^C



Prognostic Biomarkers

Negative Prognostic Factor in:

Gene	Mutation	Canine cancer	Human cancer
KIT	Internal Tandem Duplication	Mast Cell Tumor ^B	-----
TP53	p.Arg248*	Osteosarcoma ^A , Histocytic Sarcoma ^C	Yes ^A

Evidence Level Key

- ^A Validated biomarker - Proven biomarker with wide consensus and whose use is included in professional guidelines
- ^B Clinical evidence - Biomarker with consensus from experts in the field with data obtained from large, well powered studies
- ^C Case studies - Biomarker suggested by data from one or more individual case reports from clinical journals
- ^D Preclinical evidence - Biomarker suggested by data from in vivo or in vitro models

Mutation Summaries

Gene:

KIT

Mutation:

Internal Tandem Duplication

Roles in this case:  Diagnostic  Prognostic  Therapeutic**Variant Summary:**

Somatic activating KIT mutations occur in ~13-50% of canine mast cell tumors (MCTs), ~35-74% of canine gastrointestinal stromal tumors (GISTs), and ~2-8% of malignant melanomas. In MCT, mutations predominantly occur as internal tandem duplications (ITD) in KIT exons 8 and 11, leading to constitutive activation of the KIT receptor tyrosine kinase through modulation of extracellular and juxtamembrane domain regulatory activity. KIT ITDs in canine MCT have been associated with prognosis and response to tyrosine kinase inhibitors. KIT exon 11 ITDs are the most common KIT mutations in canine MCTs. This variant is a KIT exon 11 ITD.

Detailed Summary:

Please see [Link](#) for a detailed summary of this gene as well as information regarding this variant and its associated canine and human data.

Gene:

TP53

Mutation:

p.Arg248*

Roles in this case:  Diagnostic  Prognostic  Therapeutic**Variant Summary:**

Inactivating TP53 mutations (truncating mutations and/or hotspot missense mutations in the DNA-binding domain) are the most common mutations in canine and human cancers. In canine cancers, they are most commonly observed in osteosarcoma, hemangiosarcoma, and histiocytic sarcoma (>40% of cases) and less commonly (<20%) in B-cell lymphoma, pulmonary adenocarcinoma, mast cell tumors, malignant melanoma, and glioma. They are also associated with poor prognosis in many human cancers. In canine cancer cell lines, they have also been shown to correlate with resistance to the MEK inhibitor trametinib.

Detailed Summary:

Please see [Link](#) for a detailed summary of this gene as well as information regarding this variant and its associated canine and human data.

Clinical Trials Summary

Clinical Trial for this tumor type	Location	Website
TAMU-CVM Mast Cell Tumor - Prospective analysis of the anti-inflammatory and cytotoxic properties of acid suppressants on canine cutaneous mast cell tumors	Texas A&M University College Station, TX	Link

Other Clinical Trials that may be applicable

15 identified	See link for details
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Variants of Unknown Significance

The following variants were detected in [redacted] tumor sample. These variants are considered variants of uncertain significance, meaning the functional impact of the alteration on gene function is unknown or the role of the mutation in tumor diagnosis, prognosis, or treatment is unknown. Future research may reveal a role for the mutations in cancer.

No Variants of Uncertain Significance were detected in this tumor sample.

References

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15. Stengel A et al. TP53 mutations occur in 15.7% of ALL and are associated with MYC-rearrangement, low hypodiploidy, and a poor prognosis. *Blood* (2014). <https://pubmed.ncbi.nlm.nih.gov/24829203>
16. Zenz T et al. TP53 mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol* (2010). <https://pubmed.ncbi.nlm.nih.gov/20697090>

Additional Supporting Information

1. Alteration frequencies in human cancers are derived from COSMIC <https://cancer.sanger.ac.uk/> and the TCGA pan-cancer cohort, as accessed through cBioPortal <https://www.cbioportal.org/>
2. Gene summaries are based on gene descriptions provided by the National Library of Medicine and National Center for Biotechnology Information <https://www.ncbi.nlm.nih.gov/gene>
3. Mealey et al. ABCB1-1Delta polymorphism can predict hematologic toxicity in dogs treated with vincristine. *J Vet Intern Med* (2008). <https://pubmed.ncbi.nlm.nih.gov>
4. Mealey et al. Adverse drug reactions in veterinary patients associated with drug transporters. *Vet Clin North Am Small Anim Pract* (2013). <https://pubmed.ncbi.nlm.nih.gov/23890239>

Genes Evaluated by SearchLight™ DNA

SearchLight DNA™ detects multiple types of gene mutations:

- Single nucleotide variants, small nucleotide insertions and deletions (SNVs) occurring in selected commonly mutated regions in oncogenes ("Selected Exons") or in any coding region of a tumor suppressor gene ("All Coding Exons").
- Copy number variants (CNVs) including copy number gains encompassing oncogenes and copy number losses encompassing tumor suppressor genes.
- Internal tandem duplications (ITDs) occurring in oncogenes.
- Pharmacogenomic variants in genes that regulate drug processing.

	ABCB1	AKT1	AKT3	ALK	APC	ARAF	ARD1A	ASXL1	ATM	ATR	ATRX	BAP1	BRAF	BRCA1	BRCA2	BTX	CALR	CBL	CCND1	CCND2	CCND3	CCNE1	CDK12	CDK4
SNV Selected Exons	•	•	•		•							•			•	•	•	•						
SNV All Coding Exons				•		•	•	•	•		•		•	•									•	
CNV	•		•	•		•	•	•	•	•	•	•	•	•					•	•	•	•	•	•
ITD																								
Pharmacogenomic	•																							

	CDK6	CDKN2A	CDKN2B	CHEK2	CRKL	CSF3R	CTNNB1	DDR2	DNMT3A	EGFR	ERBB2	ERBB3	ESR1	ETX2	FANCA	FANCC	FANCG	FANCL	FBXW7	FGF3	FGFR1	FGFR2	FGFR3	PLCN
SNV Selected Exons						•	•	•		•			•	•		•					•	•	•	
SNV All Coding Exons		•	•	•					•		•							•						•
CNV	•	•	•	•	•				•	•	•				•	•	•	•	•	•	•	•	•	•
ITD																								
Pharmacogenomic																								

	FLT3	FOXP2	GNAQ	GNAS	GNB1	H3F3A	HRAS	IDH1	IDH2	IKZF1	JAK1	JAK2	KDR	KIT	KMT2D	KRAS	MAP2K1	MAP2K2	MAPK1	MDM2	MDM4	MEN1	MET	MLH1
SNV Selected Exons	•	•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•				•	
SNV All Coding Exons																					•			•
CNV									•				•	•	•	•		•	•	•	•	•	•	•
ITD	•													•										
Pharmacogenomic																								

	MSH2	MSH3	MSH6	MTOR	MYC	MYCN	MYD88	NF1	NF2	NFE2L2	NOTCH1	NPM1	NRAS	NTSC2	PALB2	PDGFRA	PIK3CA	PIK3R1	PIK3R2	PIM2	POLD1	POLE	PTCH1	PTEN	PTPN11
SNV Selected Exons			●	●		●			●		●	●	●		●	●	●					●		●	
SNV All Coding Exons	●	●	●				●	●		●					●				●	●	●		●		
CNV	●	●	●	●	●		●	●		●		●			●	●	●		●	●	●	●	●		
ITD																									
Pharmacogenomic																									

	RAC1	RAF1	RB1	REL	RET	RICTOR	RUNX1	SDH8	SDHD	SETD2	SF3B1	SMAD4	SMARCA4	SMARCB1	SMO	STAT3	STK11	TP53	TRAF3	TSC1	TSC2	U2AF1	VEGFA	VHL
SNV Selected Exons	•	•			•	•		•		•		•	•	•	•	•					•			
SNV All Coding Exons		•					•	•			•	•	•	•			•	•	•	•	•			•
CNV	•	•	•			•	•	•		•	•	•	•	•			•	•	•	•	•		•	•
ITD																								
Pharmacogenomic																								

Assay Description

SearchLight DNA™ detects multiple types of gene mutations:

SearchLight DNA™ is a Next Generation Sequencing targeted tumor-only assay that provides for the detection of single nucleotide variants (SNVs), small nucleotide insertions and deletions (indels), copy number variants (CNVs), internal tandem duplications (ITDs), and polymorphisms in tumor tissue. Genomic DNA is extracted from the patient's tumor samples and the isolated DNA is then prepared using a custom hybrid capture panel (Agilent). Library preparation includes shearing, purification, adaptor ligation and PCR amplification. Libraries are then clustered on a flow cell and sequenced using the Illumina MiSeq or NextSeq. Sequence data are analyzed using validated bioinformatics tools (SearchLight DNA™ Pipeline 1.2) and canine polymorphism databases. The reference genome assembly used for alignment is CanFam 3.1. Each tumor's candidate cancer-specific mutations are queried against Vidium's proprietary knowledgebase which contains thousands of canine cancer biomarker associations derived from primary peer-reviewed literature to identify potential pharmacogenomic, diagnostic, prognostic, and therapeutic associations. Additionally, this knowledgebase contains human cancer biomarker associations inferred via genomic and proteomic alignments and conservation scores from the Clinical Interpretation of Variants in Cancer (CIViC version 05/01/20) and Catalogue of Somatic Mutations in Cancer (COSMIC version 91) databases. ABCB1 germline genotype is determined based on tumor-only sequencing. SNVs are reported when present at $\geq 3\%$ allele fraction. Allele fractions are dependent on tumor purity. Tumor purity is not taken into account when calculating allele fractions. Reported CNVs (gains/losses) are identified based on comparison to a copy number baseline generated from normal tissues across major breed clades and tissue types. Reported CNVs may be focal, arm-level, or chromosome-level. ITDs are reported only for KIT and FLT3 in selected exons. Pharmacogenomic polymorphisms are reported only for ABCB1 (also known as MDR1). Indeterminate results may occur due to poor sample quality or sequencing coverage. Mean target coverage for tumor sample DNA is $\geq 200\times$ (unique reads) and $\geq 89\%$ of target bases bear $\geq 100\times$ coverage.

Limitations

Samples with a tumor content less than 30% may have reduced sensitivity and lead to false negative results. It is also possible that the sample contains a mutation below our established limit of detection or in a genetic region not included in our assay. Alterations present in repetitive or high GC content region or non-coding areas may not be detected. Indels larger than 40bp may not be detected. Copy number signal relative to background noise inherent in DNA from FFPE samples may affect sensitivity of reporting CNV gains/losses. The lack of a variant call does not necessarily indicate the absence of a variant since technical limitations to acquire data in some genetic regions may limit assay detection. ABCB1 germline genotype is inferred from tumor-only sequencing and it remains possible, though unlikely, that either ABCB1 loss of heterozygosity in the tumor or somatic acquisition of an ABCB1 mutation could interfere with accurate genotyping.

Disclaimers

This test was developed, and performance characteristics determined, by Vidium Animal Health. This test has not been approved by the U.S. FDA. The FDA has determined that such clearance or approval for veterinary diagnostics is not necessary. This test is used for clinical purposes for veterinary patients. It should also be noted that the data interpretations are based on our current understanding of genes and variants and are current as of the report date. Alterations are listed alphabetically, and not in order of strength of evidence or appropriateness for the patient's disease. When the report does identify variants with therapeutic implications, this does not promise or guarantee that a particular drug or treatment regimen will be effective or helpful in the treatment of disease in any patient, and the selection of any drug for patient treatment is done at the discretion of the treating veterinarian. These treatment options are based solely on published biomarker associations and do not include dosing, safety, or combinatorial guidelines. Please refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Use caution when combining multiple drugs and be aware of potential drug interactions. Genomic alterations should be considered in the context of the patient's history, risk factors and any previous genomic testing. Variants of Unknown Significance (VUS) may be associated with potential therapies in the future. Vidium does not update reports or send notification regarding reclassification of these alterations. Vidium Animal Health's services, including but not limited to the results contained in this report, are governed by Vidium's Terms & Conditions, which are available by email by requesting them at vidiuminfo@tgen.org.

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Electronically Signed by:



William Hendricks, PhD
Chief Scientific Officer