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Genomic Characterization of PDX Models from Rare Cancer Patients in the NCI Patient-Derived Models Repository

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INTRODUCTION

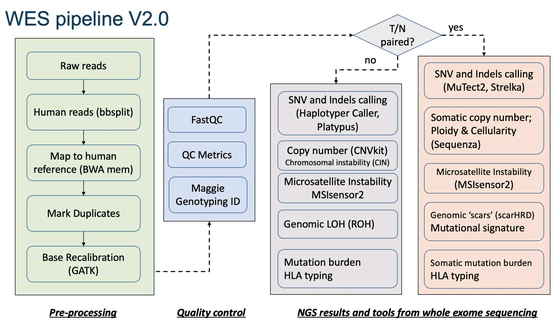
The National Cancer Institute's Patient-Derived Models Repository (NCI PDMR; https://pdmr.cancer.gov) has developed a large number of patient-derived xenograft (PDX) models from a diverse set of rare cancers[1,2,3]. These models have been genomically characterized using whole-exome sequencing (WES) and RNAseq. The resource provides a unique opportunity to explore the genomic features of rare tumor models in NCI PDMR and to understand the oncogenic processes in pre-clinical models to identify biomarkers associated with therapeutic responses.

Rare Cancer PDX Models (N=237)

Disease Body Location	Diagnosis	OncoTree Code	# of PDX models
Musculoskeletal	Non-Rhabdo. soft tissue sarcoma	SARCNOS	28
	Malignant fibrous histiocytoma/ Undifferentiated pleomorphic sarcoma	MFH/UPS	11
	Fibrosarcoma - not infantile	FIBS	8
	Synovial sarcoma	SYNS	6
	Leiomyosarcoma - uterus	ULMS	5
	Leiomyosarcoma - not uterine	LMS	5
	Ewing sarcoma/Peripheral; CIC rearranged sarcoma	ES	4
	Liposarcoma	LIPO	4
	Malig. periph. nerve sheath tum.	MPNST	4
	Osteosarcoma	OS	3
	Rhabdomyosarcoma	RMS	3
	Alveolar soft part sarcoma	ASPS	2
	Chondrosarcoma	CHS	1
Head and Neck	H & N squamous cell car., NOS	HNSC	52
	Laryngeal squamous cell carcinoma	LXSC	9
	Salivary gland cancer	SACA	6
	Nasopharyngeal carcinoma	NPC	2
Gynecologic	Ovarian epithelial cancer	OVT	10
	Carcinosarcoma of the uterus	UCS	9
	Squamous cervical cancer	CESC	4
	Female reprod. system cancer, NOS	OUTT	3
	Adenocarcinoma - cervix	CEAD	3
	Vaginal squamous cell carcinoma	VSC	3
	Uterine cancer, NOS	OUSARC	3
	Primary peritoneal carcinoma	PSEC	1
Digestive Gastrointestinal	Adenocarcinoma - small intest.	SBC	5
	Gastrointestinal stromal tumor	GIST	5
	Gastric cancer, NOS	STAD	4
	Squamous cell carcinoma - anus	ANSC	4
	Gastrointestinal cancer, NOS	APAD	2
	Cholangiocar.- intra/extrahepatic	CHOL	1
	Squamous cell car. - esophagus	ESCC	1
	Adenocarcinoma - GEJ	GEJ	1
	Liver/hepatobiliary cancer	LIVER	1
Endocrine and Neuroendocrine	Neuroendocrine cancer, NOS	NETNOS	6
	Merkel cell tumor	MCC	4
	Small cell car. (extrapulmonary)	SCUP	3
	Islet cell tumors - pancreas	PANET	1
Others	Squamous cell carcinoma - skin	CSCC	3
	Mesothelioma	MESO	2
	Adenocarcinoma, NOS	ADNOS	1
	Inflammatory breast carcinoma	IBC	1
	Adrenocortical carcinoma	ACC	1
	Hurthle cell neoplasm (thyroid)	THHC	1
	Penile squamous car.(epidermoid)	PSCC	1

METHODS

Genomic characterization was done in 4-6 PDX samples across multiple passages and lineages from each model. As the samples exhibited a high level of genomic stability within each model, consensus mutation and copy number variation (CNV), microsatellite instability (MSI), genomic loss of heterozygosity (LOH), homologous recombination deficiency score (scarHRD), and mutational signature data were generated from WES. Fusions were identified from RNASeq data using Star-Fusion and FusionInspector. Gene set enrichment analysis was conducted from the gene expression data obtained from RNASeq[4,5].



Epithelial-Mesenchymal Transition (EMT) Enrichment Score:

An EMT enrichment score of a given sample was computed from EMT signatures[6] using a two-sample Kolmogorov–Smirnov test on RNASeq gene expression data in TPM generated by RSEM[4,5].

CONCLUSION

Comprehensive genomic characterization of NCI PDMR models generated from rare cancers addresses an unmet need in the community. It will serve as a valuable resource for translational researchers interested in pre-clinical drug development and discovery.

REFERENCES

1.American Cancer Society's Cancer Facts and Figures 2020
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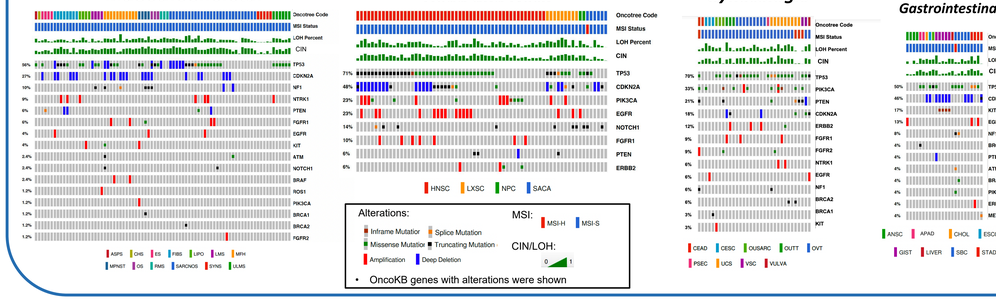
4.MoCha NGS pipeline: https://github.com/FNL-MoCha/nextgenseq_pipeline
5.Genomic profiling data, SOPs, data analysis pipeline SOPs available at NCI PDMR website
6.Tan et.al, EMBO Molecular Medicine, 2014

RESULTS

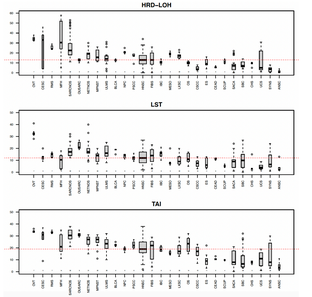
Genomic characteristic of mutations, copy number alterations, LOH, CIN and MSI



Homologous recombination deficiency through genomic 'scars' and mutational signatures

- High scarHRD scores and signature 3 were observed in ovarian cancer PDX model

PID	OncoCode	Sample	HRD-LOH	TAI	LST	HRD-sum	Purity	LOH (ROH; tumor only)
572874	OVT	572874~153-T~JY3KQ7	33	33	41	107	1	54
572874	OVT	572874~153-T~JY4KG5KZ9	34	36	32	102	1	52
572874	OVT	572874~153-T~JY4KG6	36	33	28	97	1	51
572874	OVT	572874~153-T~JY4KG7	35	33	32	100	1	52
572874	OVT	572874~153-T~JY4	32	34	31	97	1	52
572874	OVT	572874~153-T~JY5	32	34	34	100	1	51
572874	OVT	572874~153-T~ORIGINATOR	38	34	32	104	0.81	35



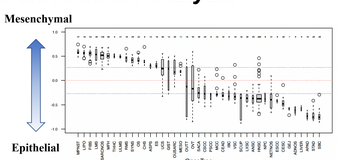
- scarHRD scores were derived from 83 PDX models (529 samples), where germline or CAF is available
- The score is highly associated with histology and is highly variable for certain cancer types
- Cancer types with high scores: OVT, CESC
- Cancer types with low scores: ANSC, SYNS
- BRCA1/2 mutational signature is highly enriched in OVT, SARCNOS, ULMS, and FIBS
- TAI and LST showed relative high correlation (R=0.69, Spearman), while HRD-LOH showed lowest correlation with LST (R=0.35)

Fusions observed in sarcoma models

Fusion	Model	# of models	# of samples
SS18-SSX1	Synovial sarcoma	3	18
ASPSCR1-TFE3	Alveolar soft part sarcoma	3	12
EWSR1-FLI1	Ewing sarcoma	2	10
NAB2-STAT6	Non-Rhabdo. Soft tissue sar.	1	6
CIC-DUX4	Ewing sarcoma; CIC rearranged sarcoma	1	5

Gene set enrichment analysis

- Epithelial-mesenchymal transition (EMT) score could accurately distinguish carcinoma from sarcoma models, confirming the divergent gene expression programs.



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