CANCER GENOMICS CONSORTIUM

Educating for Best Practices in Clinical Cancer Genomics

IntOGen – Integrative Onco Genomices

https://www.intogen.org/

http://bg.upf.edu/group/img/1-s2.0-S1535610815000574-main.pdf

http://www.nature.com/nmeth/journal/v10/n11/full/nmeth.2642.html

Home Page


intOGen
Search
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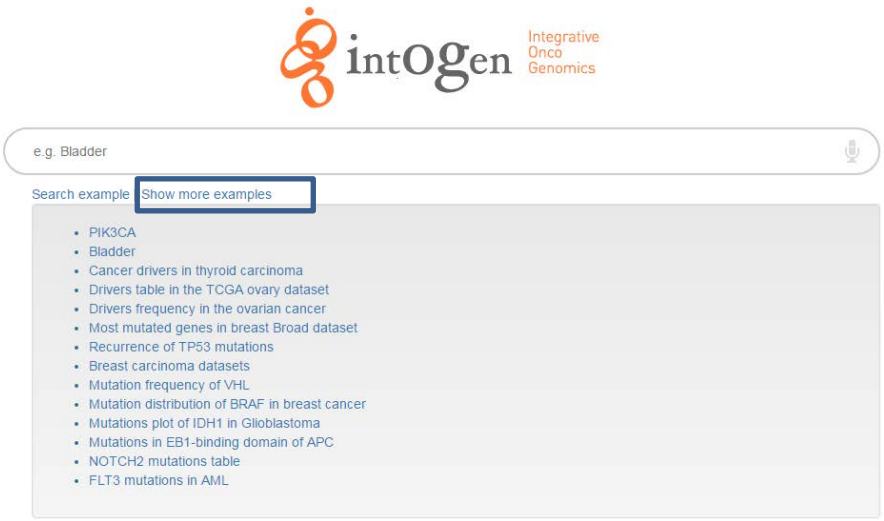
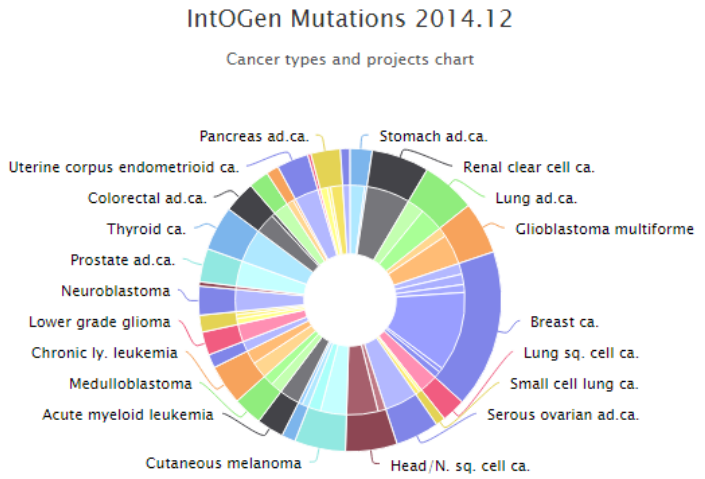
intOGen Integrative Onco Genomics
e.g. Bladder
Search example | Show more examples
Release 2014.12
Plot
Table
IntOGen Mutations 2014.12
Cancer types and projects chart
Pancreas ad.ca.
Stomach ad.ca.
Uterine corpus endometrioid ca.
Renal clear cell ca.
Colorectal ad.ca.
Lung ad.ca.
Thyroid ca.
Glioblastoma multiforme
Prostate ad.ca.
Neuroblastoma
Breast ca.
Lower grade glioma
Lung sq. cell ca.
Chronic ly. leukemia
Small cell lung ca.
Medulloblastoma
Serous ovarian ad.ca.
Acute myeloid leukemia
Cutaneous melanoma
Head/N. sq. cell ca.
Cancer Types 28
Projects 48
Samples 6792
Somatic mutations 1341752
Coding sequence mutations (CSMs)
in driver genes 21648
in all genes 1341706
Protein affecting mutations (PAMs)
in driver genes 18649
in all genes 603770
IntOGen collects and analyses somatic mutations in thousands of tumor genomes to identify cancer driver genes.
Feedback & Support

Search Bar

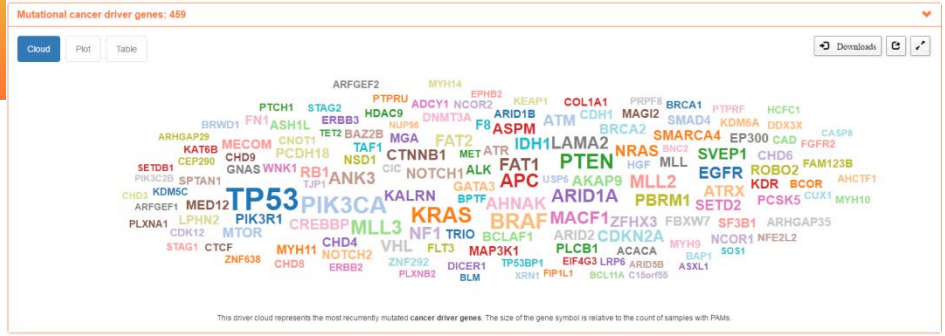
- Examples provided for effective searches
- Home Page depicts cancer types with information in IntOGen
  - Pie chart or Table format
  - Can use this information to create effective search

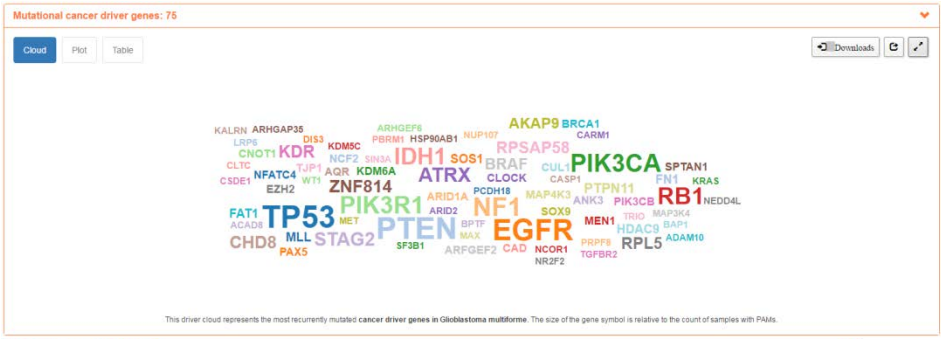


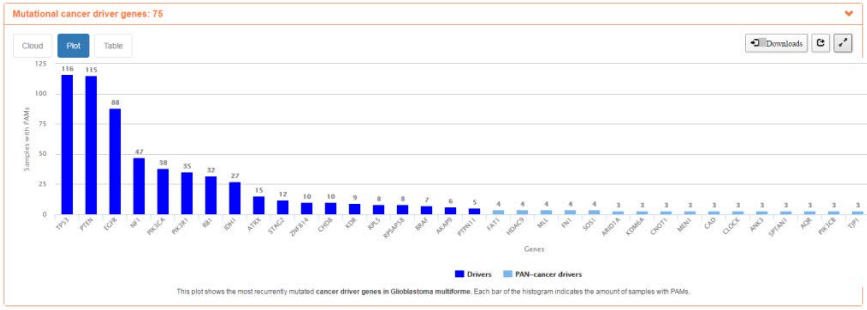


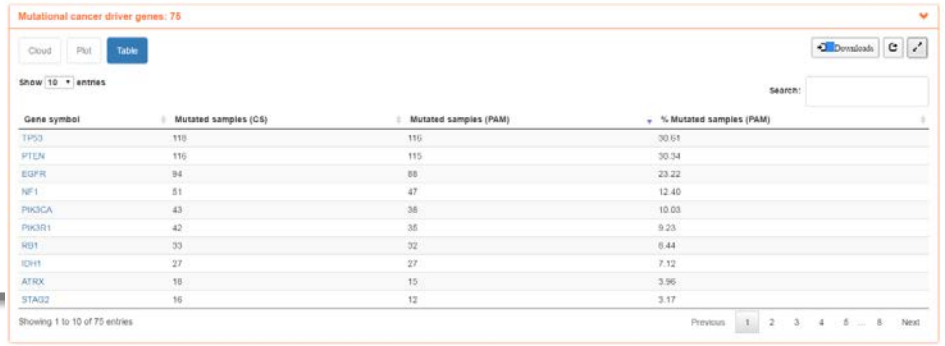
Mutational Cancer Drivers

- Home page shows word cloud with the most frequently mutated cancer driver genes. (top right)
- Narrow search to see disease-specific cloud
  - Glioblastoma Multiforme (GBM) depicted on middle right
- Log in to download
  - Can sign up with Google Account
- Data is able to be saved
- View Data as Word Cloud, bar graph or table









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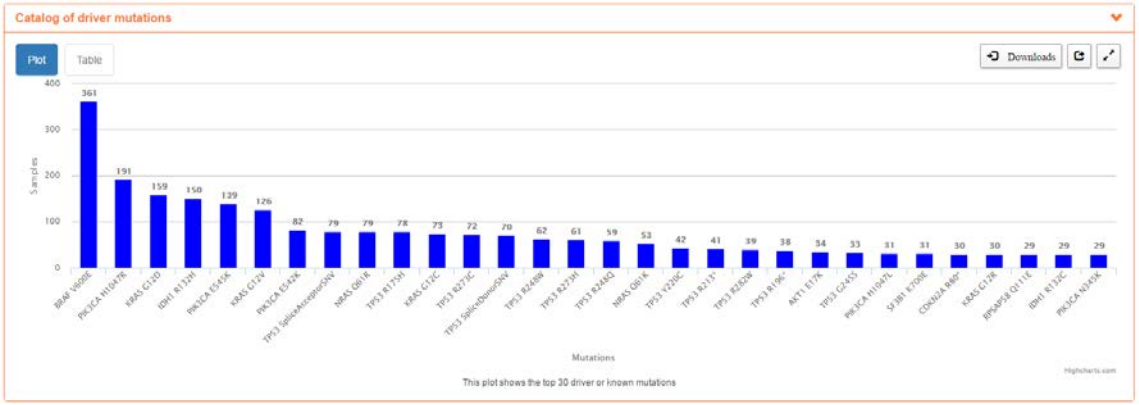
Educating for best practices in clinical cancer genomics

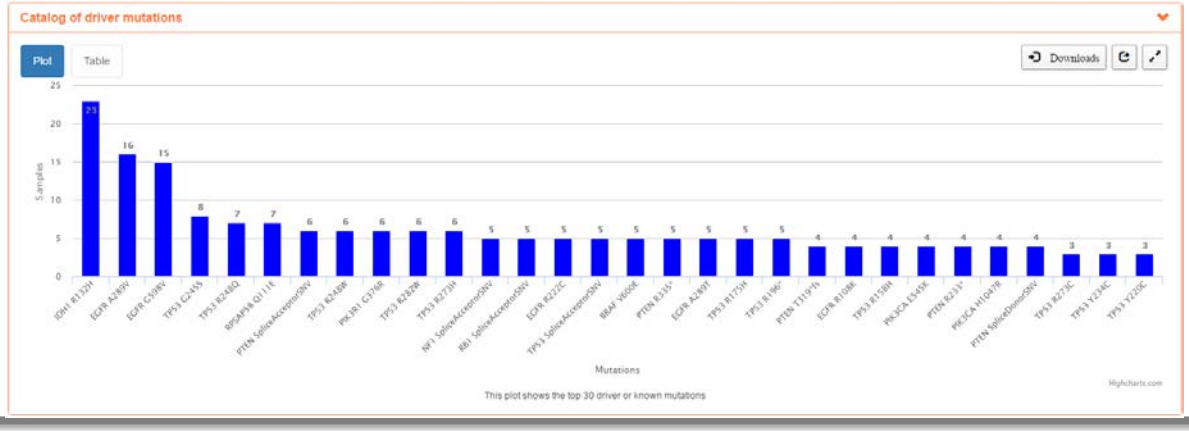
Mutation Data and Driver Determination

- Tumor mutation data: from large projects (ICGC, TCGA, other publications).
- Driver Mutation Identification: Classification done in silico using a number of tools
  - OncodriveFM: http://bg.upf.edu/group/projects/oncodrive-fm.php
  - OncodriveCLUST: http://bg.upf.edu/group/projects/oncodrive-clust.php
  - MutSigCV: http://archive.broadinstitute.org/cancer/cga/mutsig
  - OncodriveROLE: http://bg.upf.edu/oncodrive-role/

Catalog of Driver Mutations



- On Home Page (above), this table shows a Pan Cancer view of specific driver mutations.
- On Disease Specific page (below is table for GBM), this table shows driver mutations within your selected disease
  - Log in to download or save data.



Projects Table

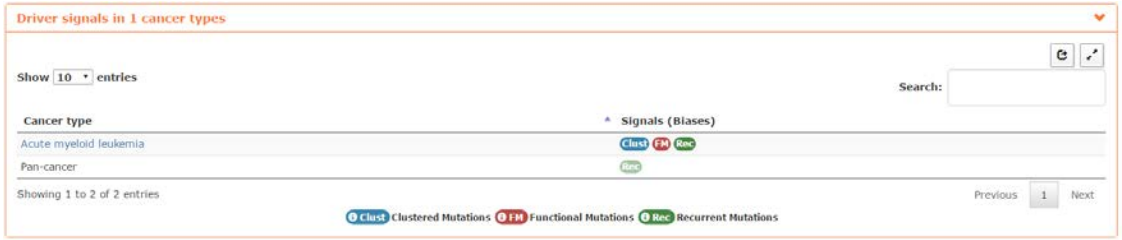
- On resulting page from search, this table is available
  - Links to project page (with information from that source) and links to project publications

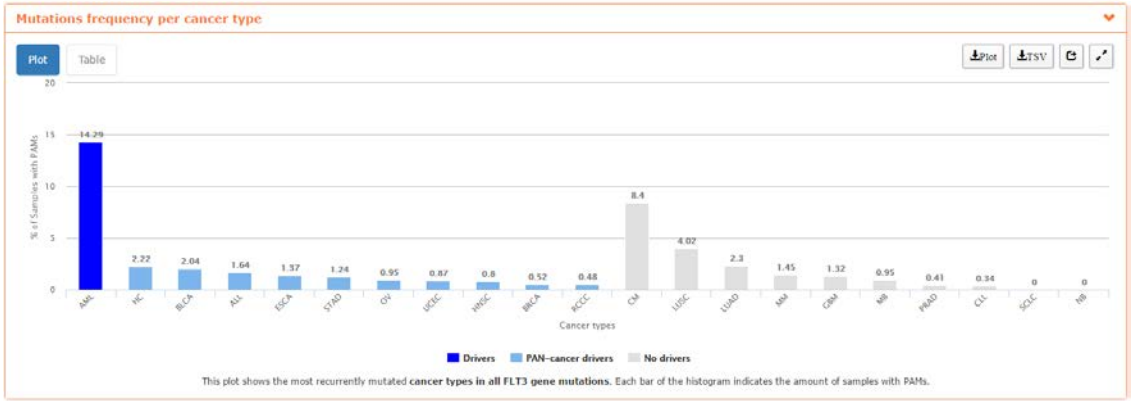
Search for Gene

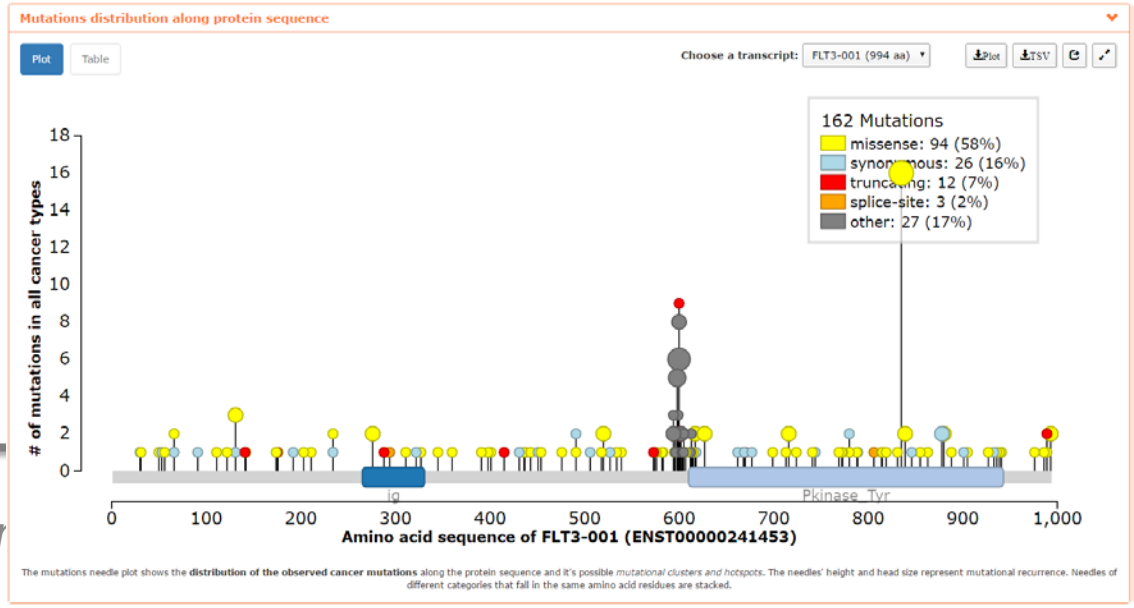
- Summary
- Gene Details
- Driver List
- Mutations per Cancer Type
- Mutations along protein sequence

Search for Gene

- Summary
- Gene Details
- Driver List
- Mutations per Cancer Type
  - Log in to download as .png or .csv
- Mutations along protein sequence
  - Can view different transcripts
  - Log in to download as .png or .csv

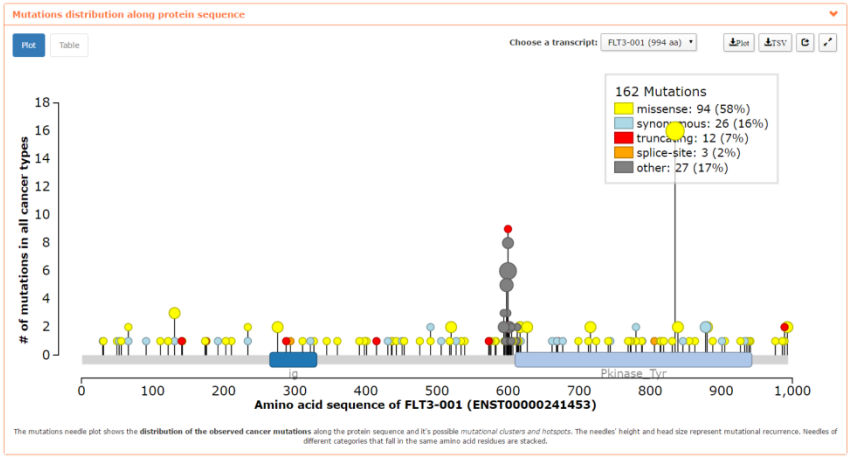


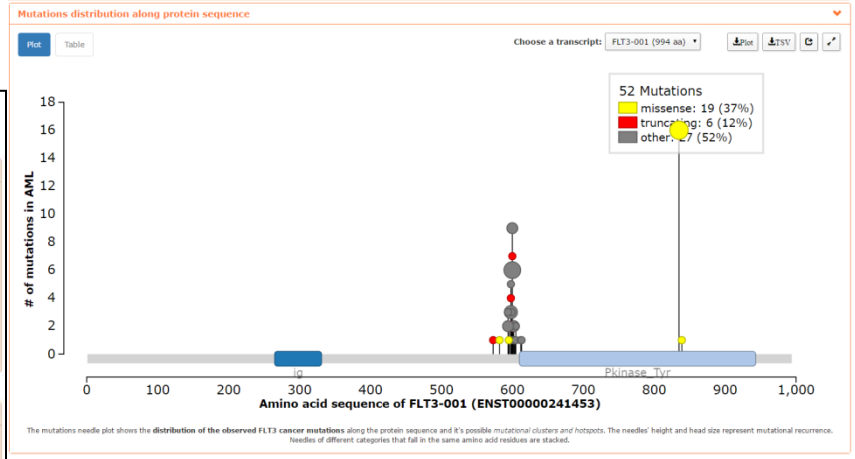


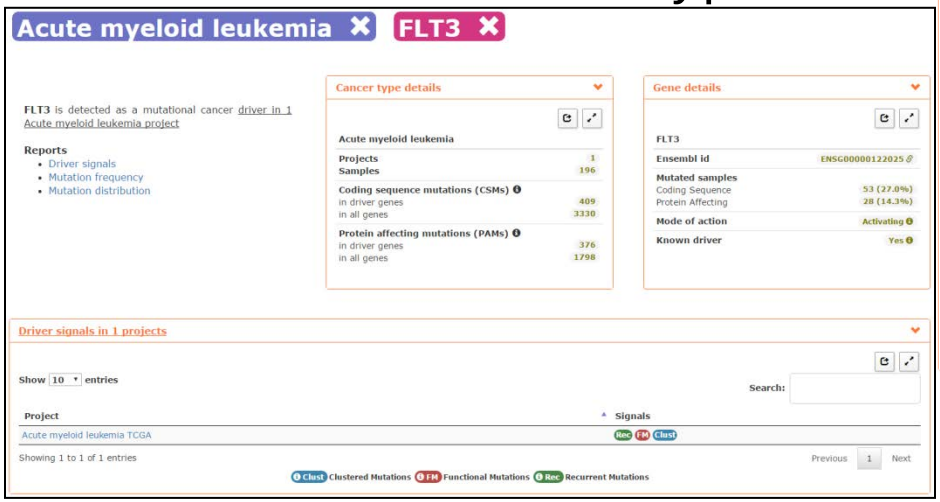


Add Disease to Search Criteria

- Refines search criteria to only include mutations involved in cancer type specified.
  - Top right – all FLT3 mutations
  - Bottom right – FLT3 filtered for disease type





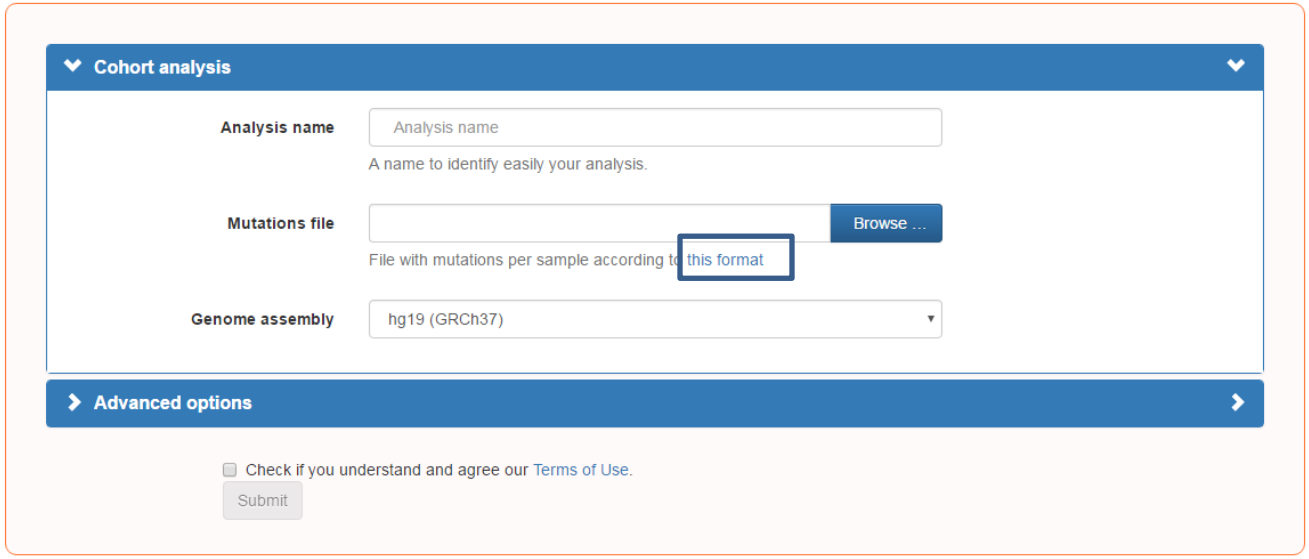


Downloads Page

- Log into account to download databases
  - **Catalog of Driver Mutations (2016.5)**
    - Results of driver analysis using Cancer Genome Interpreter (See separate slide deck) and OncodriverMUT
    - *Tamborero D., Rubio-Perez C., Deu-Pons J., Schroeder M., Vivancos A., Rovira A., Tusquets I, Albanell J., Rodon J., Tabernero J., Dienstmann R., Gonzalez-Perez A. and Lopez-Bigas N.* ***Cancer Genome Interpreter identifies driver and actionable alterations****. Manuscript in preparation*
  - **Cancer Drivers Database (2014.12)**
    - In silico prescription of drugs based on somatic mutations
    - *Rubio-Perez, C., Tamborero, D., Schroeder, MP., Antolín, AA., Deu-Pons,J., Perez-Llamas, C., Mestres, J., Gonzalez-Perez, A., Lopez-Bigas, N. In silico prescription of anticancer drugs to cohorts of 28 tumor types reveals novel targeting opportunities. Cancer Cell 27 (2015), pp. 382-396*
  - **Cancer Driver Actionability Database (2014.12)**
    - Drug Interactions data in Cancer Drivers Database
    - *Rubio-Perez, C., Tamborero, D., Schroeder, MP., Antolín, AA., Deu-Pons,J., Perez-Llamas, C., Mestres, J., Gonzalez-Perez, A., Lopez-Bigas, N. In silico prescription of anticancer drugs to cohorts of 28 tumor types reveals novel targeting opportunities. Cancer Cell 27 (2015), pp. 382-396*
  - **TCGA pan-cancer12 high confidence drivers (2013)**
    - *doi:10.1038/srep02650*
  - **Cancer driver database (2013)**
    - *doi:10.1038/nmeth.2642*
  - **IntOGen Arrays (2010)**
    - *doi:10.1038/nmeth0210-92.*

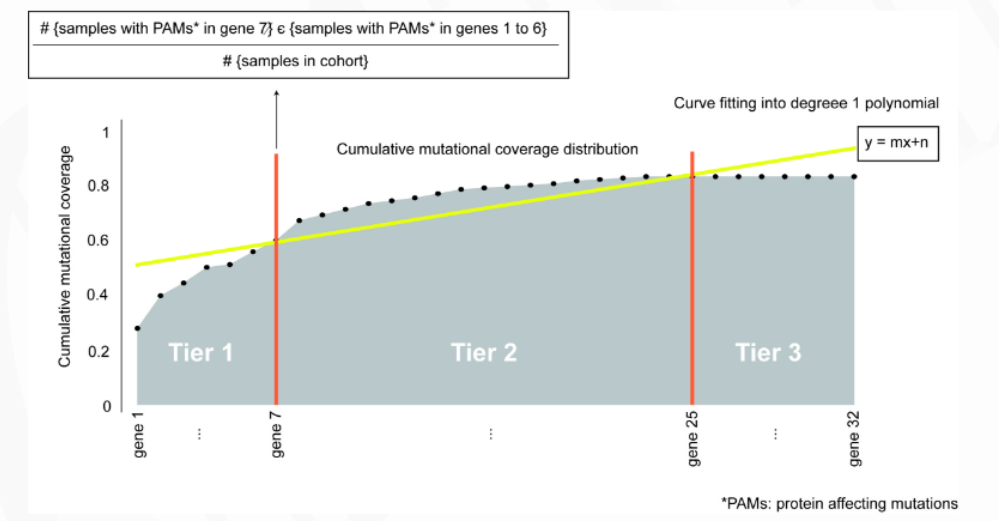
Analysis Page

- Log in to run your own mutations list through the IntOGen pipeline by uploading a mutations file.
  - Make sure file is formatted to specifications in link

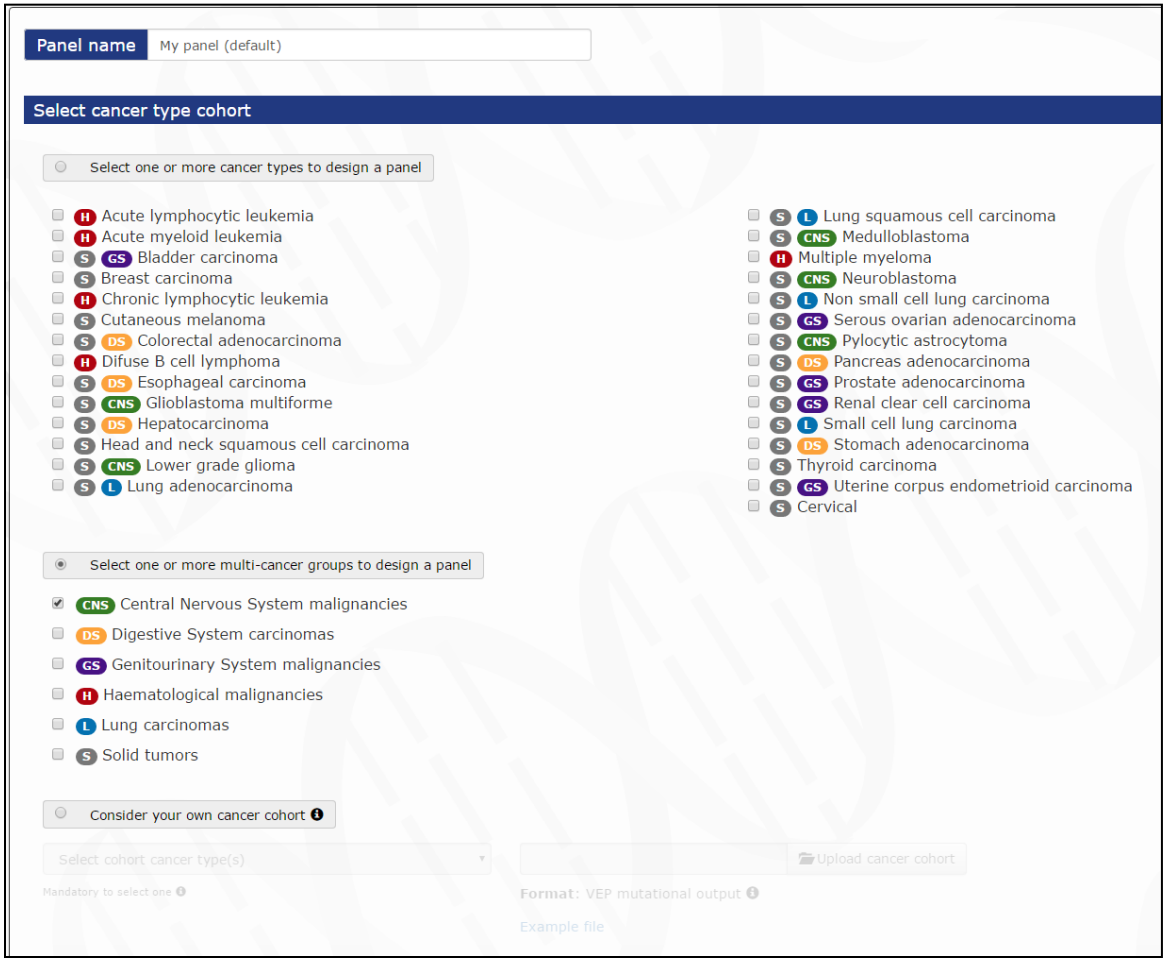


OncoPaD

- http://www.intogen.org/oncopad
- Resource specifically designed to help design cost-effective NGS panels
  - Maximizing sample coverage
  - Minimizing the amount of DNA to sequence – focus on mutation hotspots, regulatory domains
- Need Google Account to design panel



Design Page – Select Cancer type cohort

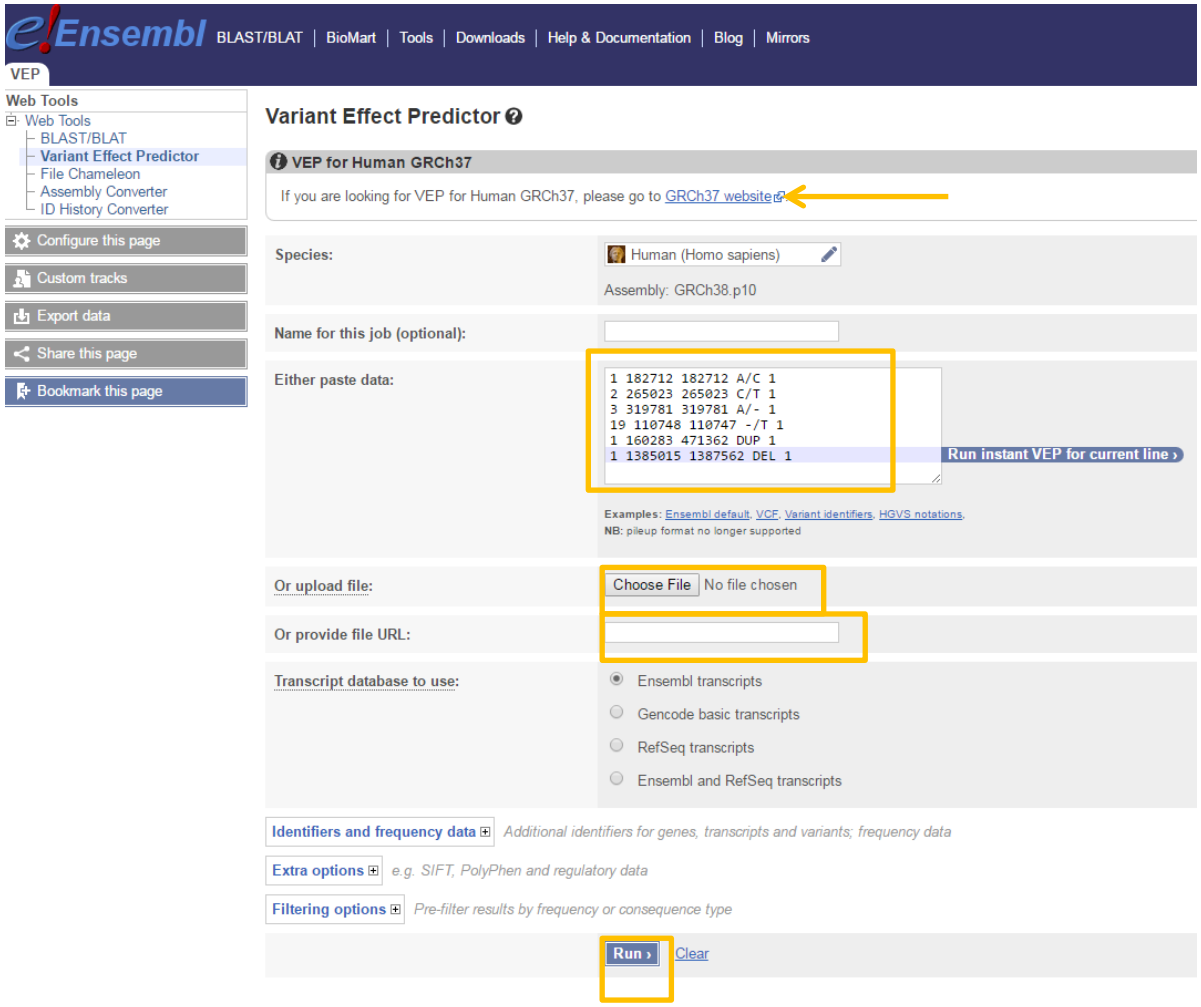


- 28 cancer types to pick from in top menu
  - Can select multiple options in this menu
- 6 multi-cancer group to pick from in bottom menu
  - Can select multiple options in this menu
- Or Consider your own cancer cohort
- You can only select one menu from which to select a cohort.

Consider your own cancer cohort

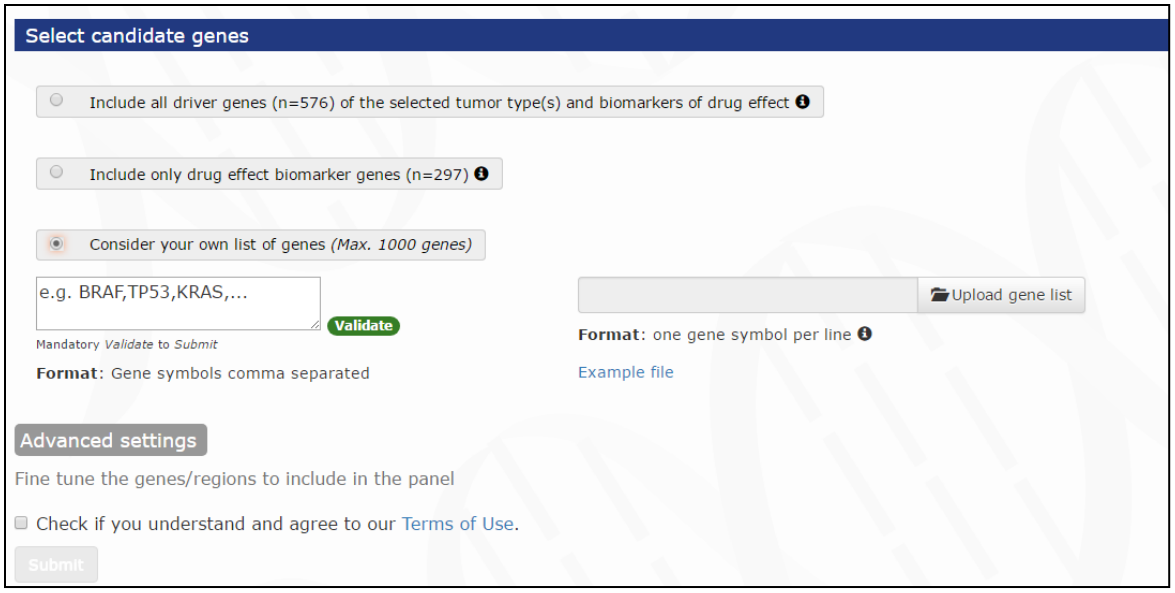
- Select cohort cancer type from drop down list.
- Create/input VEP (Variant Effect Predictor) mutation file
  - TXT file generated from http://www.ensembl.org/Tools/VEP
    - To generate file on Ensembl site, you must use one of the following formats for your variants
      - Ensembl default: 1 1385015 1387562 DEL 1
      - VCF: 1 1385015 sv2 . <DEL> . . SVTYPE=DEL;END=1387562
      - Variant identifiers: RCV000004642
      - HGVS notations: LRG_101t1:c.1019T>C

Creating VEP file



- Can paste, upload mutations file or provide file URL to create VEP
- Select correct gene transcript set
- Make sure you are using the correct genome build (hg37 vs hg38)
- Select “Run”
- Save resulting file to input into design pad in OncoPaD.

OncoPaD design page – Select candidate genes



- Select candidate genes for panel.
  - All driver genes and biomarkers of drug effect for selected tumor type
  - Only drug effect biomarkers
  - Custom list of genes
    - Validate gene symbols from your list prior to uploading
  - Check box for understanding Terms of Use
  - Click ‘Submit’

OncoPaD design page – Advanced Settings

- Specify panel size
- Include/Exclude panel gene candidates
- Fine tune panel tier gene classification (See graph on slide 13)
  - Tier 1: Contribute most to cumulative mutational coverage
  - Tier 2: Contribute less to cumulative mutational coverage
  - Tier 3: Genes do not contribute to cumulative mutational coverage
- Fine tune gene regions parameters

- See screenshot on next page.


intOgen
Specify a panel size
Maximum number of genes to include in the panel
e.g. 20 (not limited by default)
Maximum Kpbs of DNA to sequence in the panel
e.g. 100 (not limited by default)
Include/exclude panel gene candidates
*Only if one of the pre-compiled gene lists was selected as input
Specify if you want to force including one/several genes into the panel candidates
e.g. BRAF,TP53,KRAS,...
Upload gene list
File format: one gene symbol per line
Format: gene symbols comma separated
Specify if you want to force excluding one/several genes from the panel candidates
e.g. JAK1,JAK2,...
Upload gene list
File format: one gene symbol per line
Format: gene symbols comma separated
Fine tune panel tier gene classification
In this section you can modify the gene tier classification method.
Tick to consider Tier 1 stringent classification.
Fine tune gene regions parameters
In this section you can fine-tune whether genes are included in full or by specific regions of high mutation density in the panel.
At least 80% of the mutations in a gene are demanded to be allocated in mutation high density regions, modify this parameter here.
Specify if some genes should be included as whole genes and not regions in the panel (by default only TP53 is included whole gene):
TP53
Upload gene list
File format: one gene symbol per line
Format: gene symbols comma separated
Tick to include all genes in the panel as whole genes, do not consider gene regions.

Results page

Can download results in different formats

BED file | Print/PDF report | Excel file

My Panel was designed to interrogate Glioblastoma multiforme (GBM), Lower grade glioma (LGG), Medulloblastoma (MB), Neuroblastoma (NB) and Pylocytic astrocytoma (PA) tumors. 141 genes were in the input to generate the panel.

My Panel (only Tier 1 genes) would contain 45.88 DNA Kbps and include 19 genes/gene fragments; it would identify 45.0% of the 1069 tumors in the cohort.

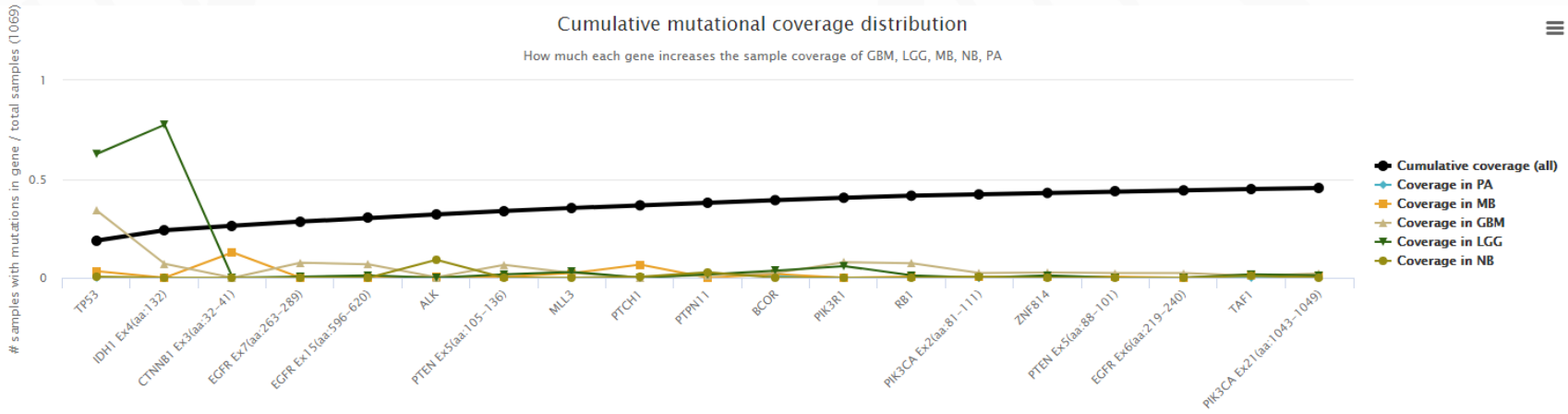
My Panel summary

Cancer Types	GBM, LGG, MB, NB, PA
Samples available for analysis	1069
Tier 1 genes/regions	
number of genes/regions	19
maximum mutational coverage	45.0%
Tier 2 genes/regions	
number of genes/regions	65
maximum mutational coverage	60.0%

Can view gene plots in graph format or all genes in table format

My Panel mutational coverage

Tier 1 cumulative plot | Tier 2 cumulative plot | Table



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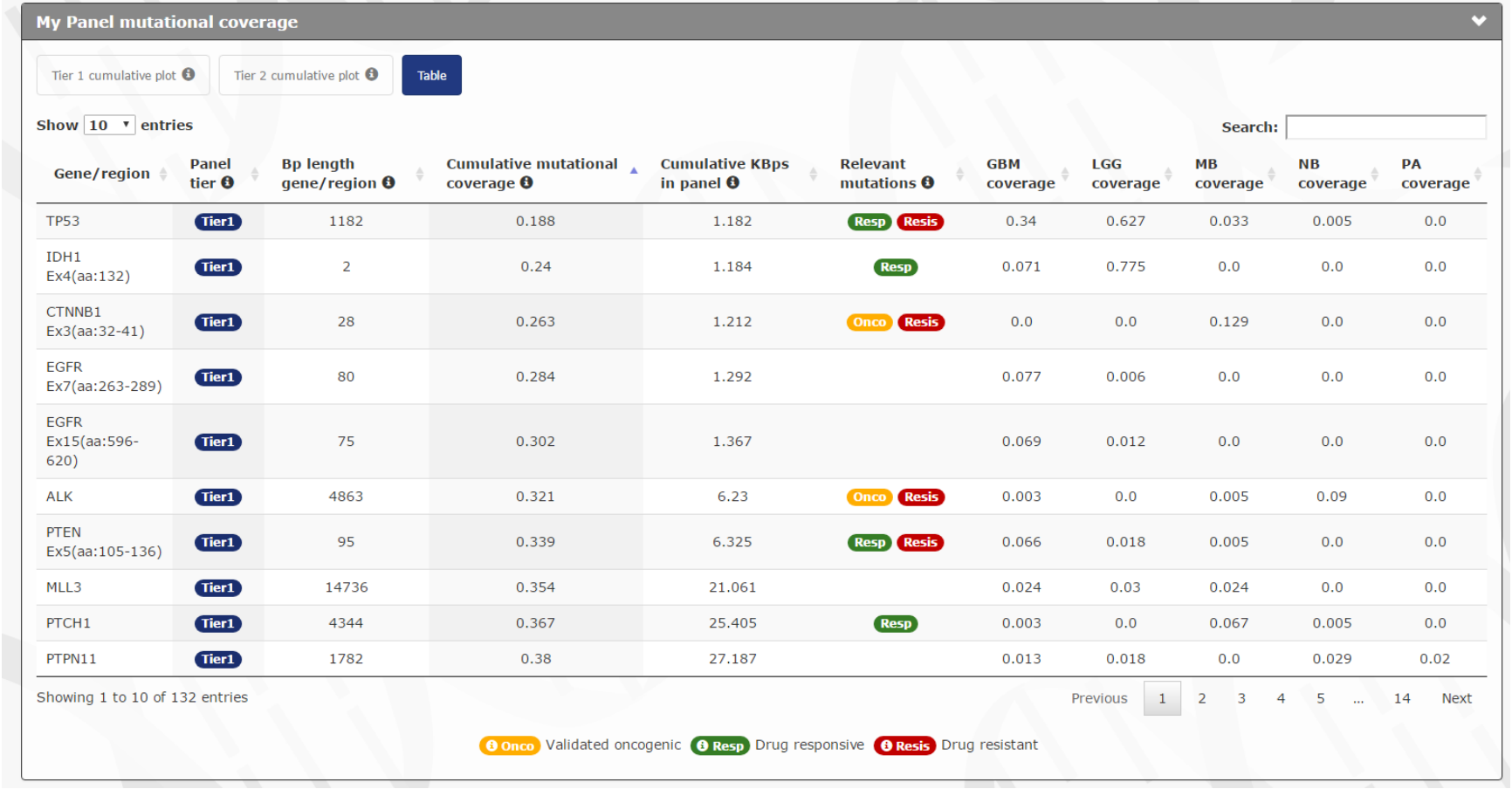
Panel Mutational Coverage



My Panel mutational coverage

Tier 1 cumulative plot | Tier 2 cumulative plot | Table

Show 10 entries Search:

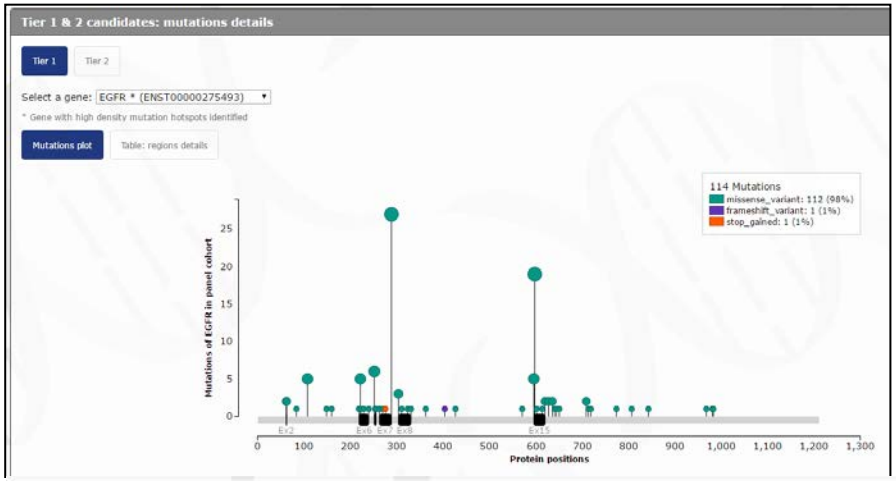
Gene/region	Panel tier	Bp length gene/region	Cumulative mutational coverage	Cumulative KBps in panel	Relevant mutations	GBM coverage	LGG coverage	MB coverage	NB coverage	PA coverage
TP53	Tier1	1182	0.188	1.182	Resp Resis	0.34	0.627	0.033	0.005	0.0
IDH1 Ex4(aa:132)	Tier1	2	0.24	1.184	Resp	0.071	0.775	0.0	0.0	0.0
CTNNB1 Ex3(aa:32-41)	Tier1	28	0.263	1.212	Onco Resis	0.0	0.0	0.129	0.0	0.0
EGFR Ex7(aa:263-289)	Tier1	80	0.284	1.292		0.077	0.006	0.0	0.0	0.0
EGFR Ex15(aa:596-620)	Tier1	75	0.302	1.367		0.069	0.012	0.0	0.0	0.0
ALK	Tier1	4863	0.321	6.23	Onco Resis	0.003	0.0	0.005	0.09	0.0
PTEN Ex5(aa:105-136)	Tier1	95	0.339	6.325	Resp Resis	0.066	0.018	0.005	0.0	0.0
MLL3	Tier1	14736	0.354	21.061		0.024	0.03	0.024	0.0	0.0
PTCH1	Tier1	4344	0.367	25.405	Resp	0.003	0.0	0.067	0.005	0.0
PTPN11	Tier1	1782	0.38	27.187		0.013	0.018	0.0	0.029	0.02

Showing 1 to 10 of 132 entries Previous 1 2 3 4 5 ... 14 Next

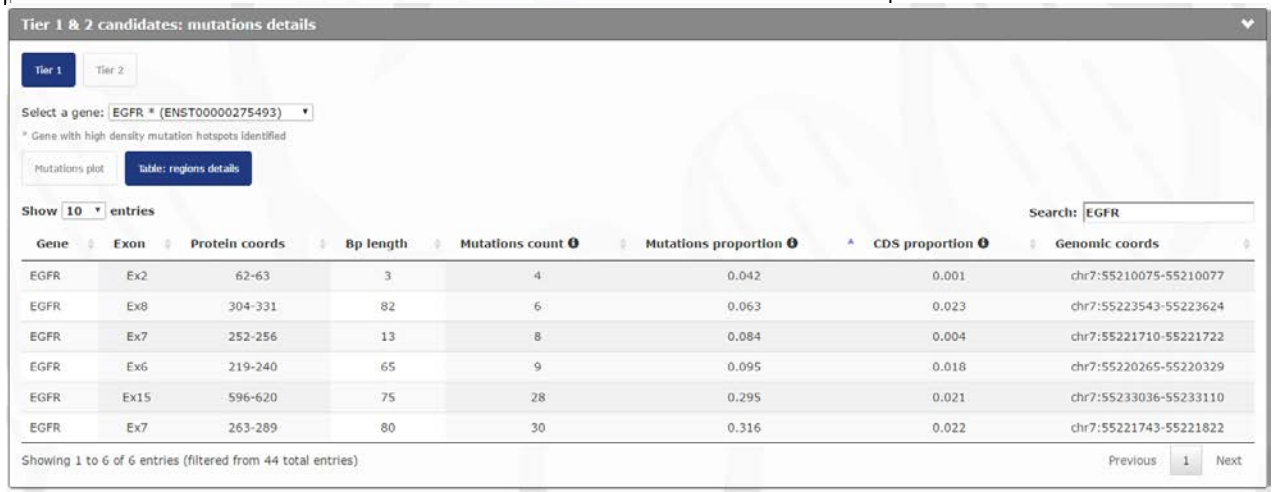
Onco Validated oncogenic Resp Drug responsive Resis Drug resistant

* The next collapsed table below this one is the panel mutational coverage considering more than one gene per sample.

Tier 1 & 2 candidates: mutations details



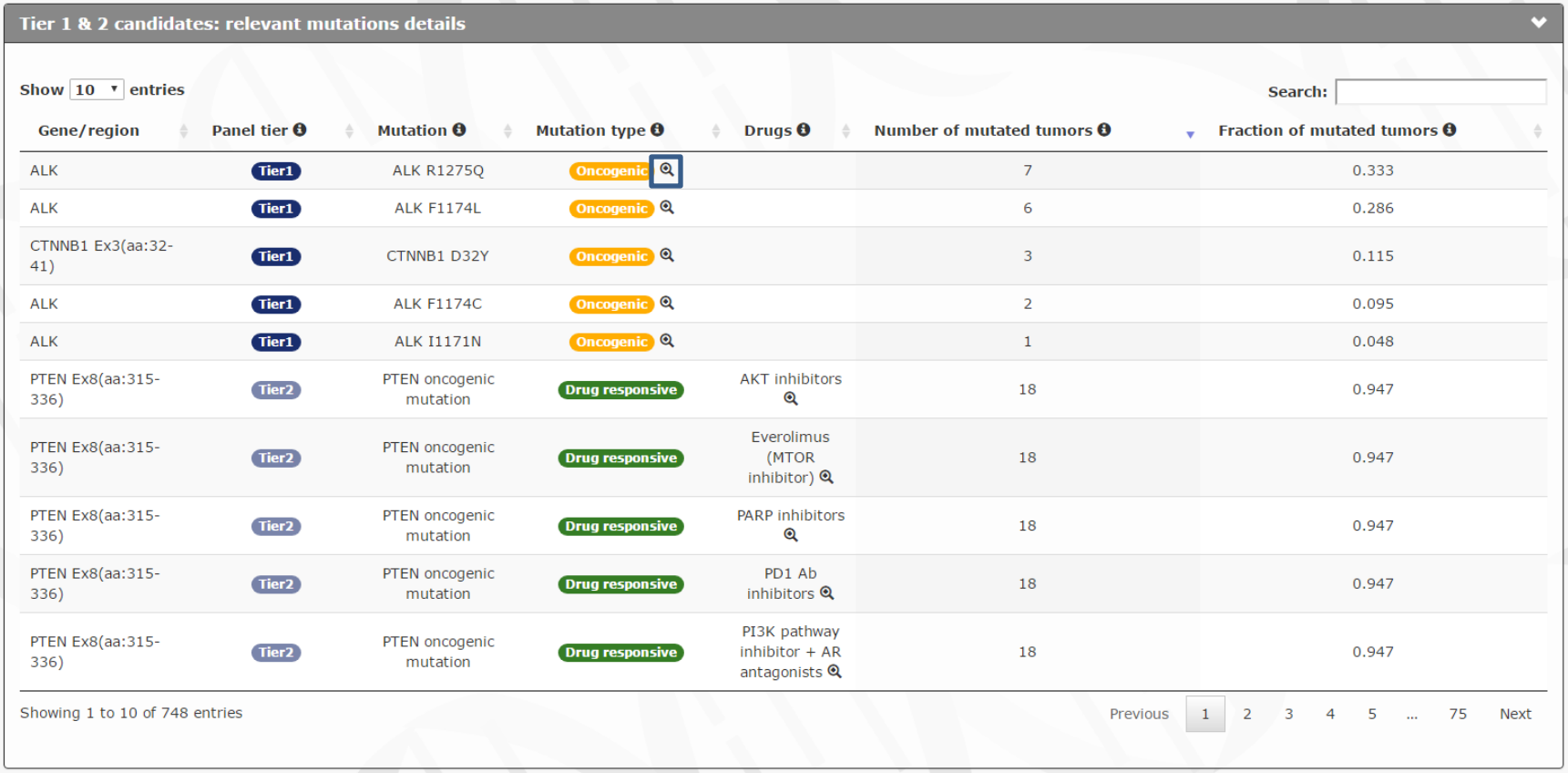
- Mutations observed per panel gene in visual gene transcript with mutation markers
- Table with mutations described in more detail including genomic coordinates



Gene	Exon	Protein coords	Bp length	Mutations count	Mutations proportion	CDS proportion	Genomic coords
EGFR	Ex2	62-63	3	4	0.042	0.001	chr7:55210075-55210077
EGFR	Ex8	304-331	82	6	0.063	0.023	chr7:55223543-55223624
EGFR	Ex7	252-256	13	8	0.084	0.004	chr7:55221710-55221722
EGFR	Ex6	219-240	65	9	0.095	0.018	chr7:55220265-55220329
EGFR	Ex15	596-620	75	28	0.295	0.021	chr7:55233036-55233110
EGFR	Ex7	263-289	80	30	0.316	0.022	chr7:55221743-55221822

Showing 1 to 6 of 6 entries (filtered from 44 total entries)
Previous 1 Next

Tier 1 & 2 candidates: relevant mutations details



Tier 1 & 2 candidates: relevant mutations details

Show 10 entries — Search:

Gene/region	Panel tier	Mutation	Mutation type	Drugs	Number of mutated tumors	Fraction of mutated tumors
ALK	Tier1	ALK R1275Q	Oncogenic		7	0.333
ALK	Tier1	ALK F1174L	Oncogenic		6	0.286
CTNNB1 Ex3(aa:32-41)	Tier1	CTNNB1 D32Y	Oncogenic		3	0.115
ALK	Tier1	ALK F1174C	Oncogenic		2	0.095
ALK	Tier1	ALK I1171N	Oncogenic		1	0.048
PTEN Ex8(aa:315-336)	Tier2	PTEN oncogenic mutation	Drug responsive	AKT inhibitors	18	0.947
PTEN Ex8(aa:315-336)	Tier2	PTEN oncogenic mutation	Drug responsive	Everolimus (MTOR inhibitor)	18	0.947
PTEN Ex8(aa:315-336)	Tier2	PTEN oncogenic mutation	Drug responsive	PARP inhibitors	18	0.947
PTEN Ex8(aa:315-336)	Tier2	PTEN oncogenic mutation	Drug responsive	PD1 Ab inhibitors	18	0.947
PTEN Ex8(aa:315-336)	Tier2	PTEN oncogenic mutation	Drug responsive	PI3K pathway inhibitor + AR antagonists	18	0.947

Showing 1 to 10 of 748 entries — Previous 1 2 3 4 5 ... 75 Next

- Click on magnifying glass or hover over mutation type to see details and/or references for the information in the table.
- Click over "i" in column headings to see description of information supplied in column

Tier 1 & 2 candidates: general features

- Provides mode of action, supporting reference, and cancer (in your query) for which the gene has been identified

Tier 1 & 2 candidates: general features

Show 10 entries Search:

Gene	Panel tier	Driver mode of action	Driver source	Major driver
ALK	Tier1	Activating	Rubio-Perez&Tamborero(2015), CGC, Validated somatic mutation list	
BCOR	Tier1	Loss of function	Rubio-Perez&Tamborero(2015)	
MLL3	Tier1	Loss of function	Rubio-Perez&Tamborero(2015)	
PIK3R1	Tier1	Loss of function	Rubio-Perez&Tamborero(2015), CGC	
PTCH1	Tier1	No class	Rubio-Perez&Tamborero(2015), CGC	
PTPN11	Tier1	Activating	Rubio-Perez&Tamborero(2015)	
RB1	Tier1	Loss of function	Rubio-Perez&Tamborero(2015)	GBM
TAF1	Tier1	Activating	Rubio-Perez&Tamborero(2015)	
TP53	Tier1	Loss of function	Rubio-Perez&Tamborero(2015), CGC, Validated somatic mutation list	LGG,GBM
ZNF814	Tier1	Activating	Rubio-Perez&Tamborero(2015)	

Showing 1 to 10 of 54 entries Previous 1 2 3 4 5 6 Next

OncoPaD Literature

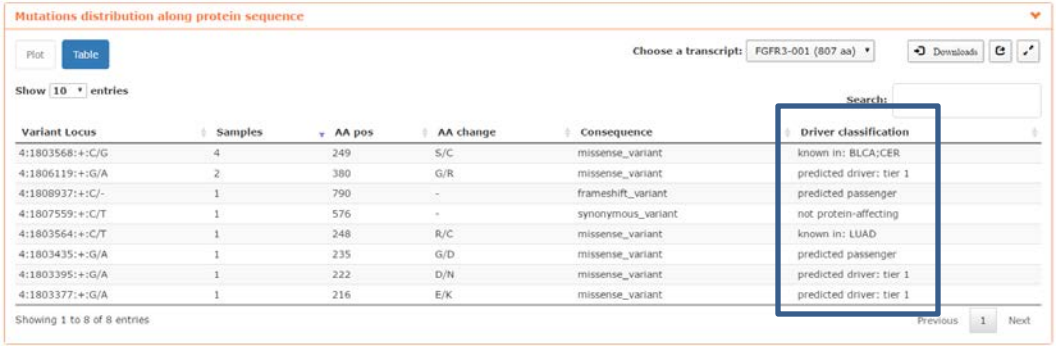
- https://www.ncbi.nlm.nih.gov/pubmed/25759023
- https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0349-1

Scenario #1

- You are interpreting an NGS panel for bladder cancer and have encountered the missense mutations below. Which of these are driver mutations according to IntOGen?
  - FBXW7 T305K
  - TP53 R248K
  - ARID1A Q2188H
  - FGFR3 G237D

Scenario #1

- Select the criteria “Bladder carcinoma” and “Gene of interest”
- Scroll down to “Mutations distribution along protein sequence” and toggle to Table view.
- Find variant of choi… “…i… classification” colu…



- FBXW7 T305K - Drive…
- TP53 R248K - Driver
- ARID1A Q2188H - Passenger
- FGFR3 G237D – No data available

Scenario #2

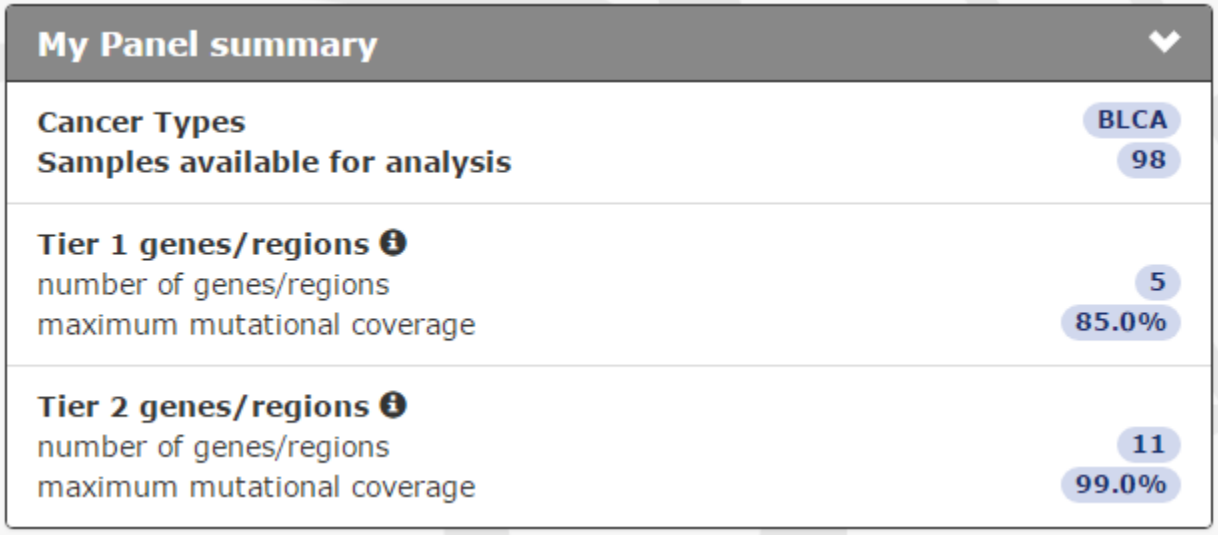
- You are creating an NGS panel for Bladder cancer.
  - Use OncoPaD tool to find candidate NGS targets.

Scenario #2: Panel Design

- Select Bladder carcinoma as your target cancer type cohort.
- Select candidate gene pool
  - All driver genes of the selected tumor type and biomarkers of drug effect
- Under Advanced Settings – can specify a maximum number of genes/regions you want in your panel if applicable.

Scenario #2: Results

- 16 regions were identified as either Tier 1 or Tier 2 mutation regions.



My Panel was designed to interrogate Bladder carcinoma (BLCA) tumors. 159 genes were in the input to generate the panel.

The total number of genes included in the panel was set by user to 25.

My Panel (only Tier 1 genes) would contain 36.1 DNA Kbps and include 5 genes/gene fragments; it would identify 85.0% of the 98 tumors in the cohort.

NGS Panel Creation Results

Tier 1 Genes/Regions

- TP53
- MLL2
- ARID1A
- KDM6A
- EP300

- Green = information regarding gene mutations and response to therapy

Tier 2 Genes/Regions

- FGFR3 – exon 7
- NUP107
- MLL3
- ZNF814 – exon 3
- CUL2
- BCLAF1
- PCDH18
- TSC1
- SMC1A
- CEP290
- GPS2

Scenario #3

- Your institution is creating a list of genomic HotSpots for mutations (SNVs)
  - All oncology samples
  - Specific diseases (i.e. AML)

- Use "Catalog of driver mutations" to navigate driver mutations seen frequently in cancer.

Scenario 3A

- Pan Cancer Mutation HotSpots
- From homepage scroll down to "Catalg of driver mutations" section and toggle to table view.
- Determine appropriate percentage of samples with mutations to add to list.
- Log in to download list as .csv

Scenario 3B

- AML Mutation HotSpots
- Select 'AML – Acute Myeloid Leukemia' from the search bar
- Scroll down to "Catalog of driver mutations" and toggle to table view.
  - Visible list will include all mutations seen in at least 4 samples, but downloaded list will include more.

Contact Information

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