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GenViz Module 5: Variant annotation and interpretation

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Genomic Data Visualization and Interpretation
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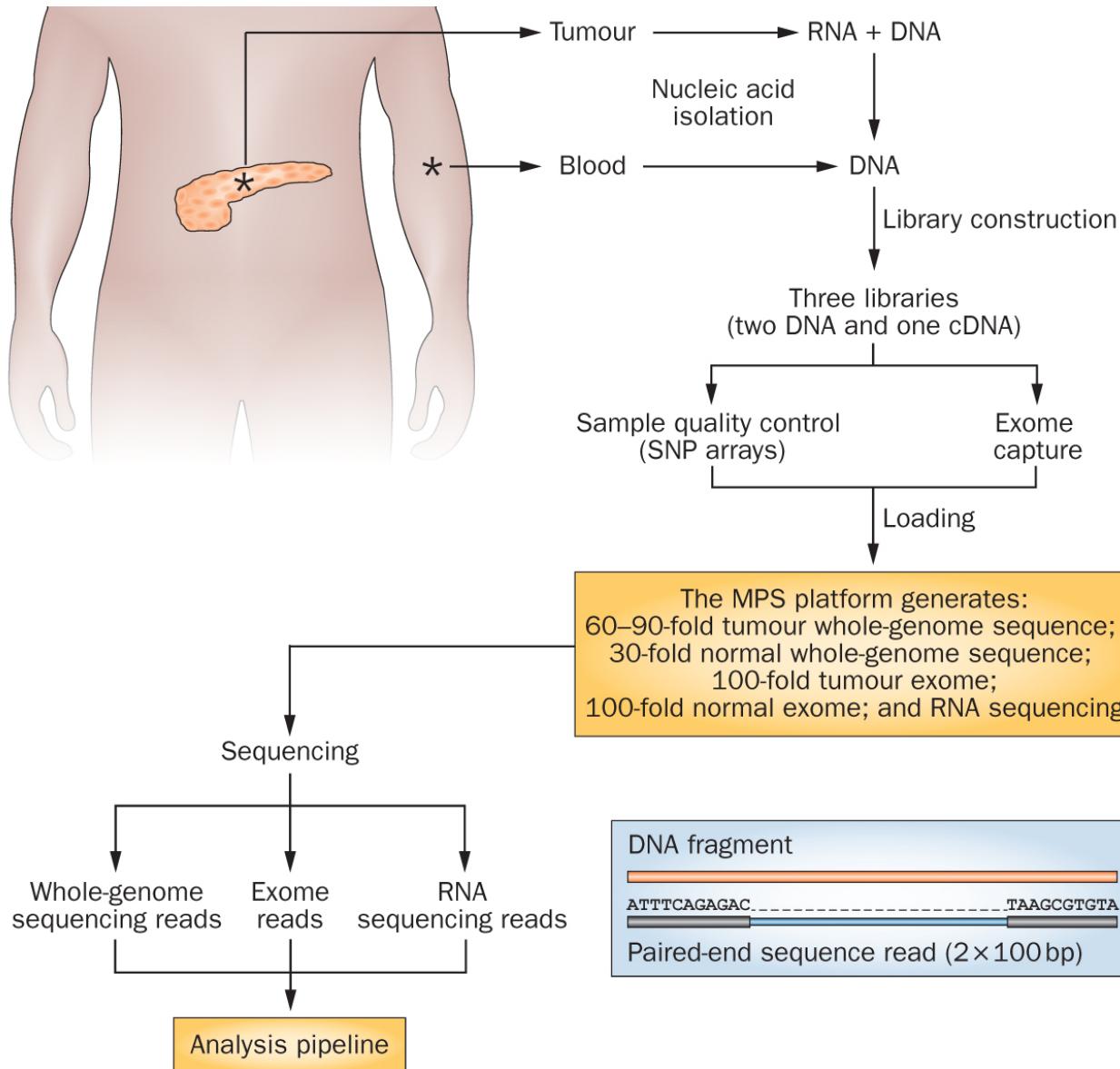
Learning objectives of the course

- **Module 1: Introduction to genomic data visualization and interpretation**
- **Module 2: Using R for genomic data visualization and interpretation**
- **Module 3: Introduction to GenVisR**
- **Module 4: Expression profiling, visualization, and interpretation**
- **Module 5: Variant annotation and interpretation**
- **Module 6: Q & A, discussion, integrated assignments, and working with your own data**
- **Tutorials**
 - Provide working examples of data visualization and interpretation
 - Self contained, self explanatory, portable

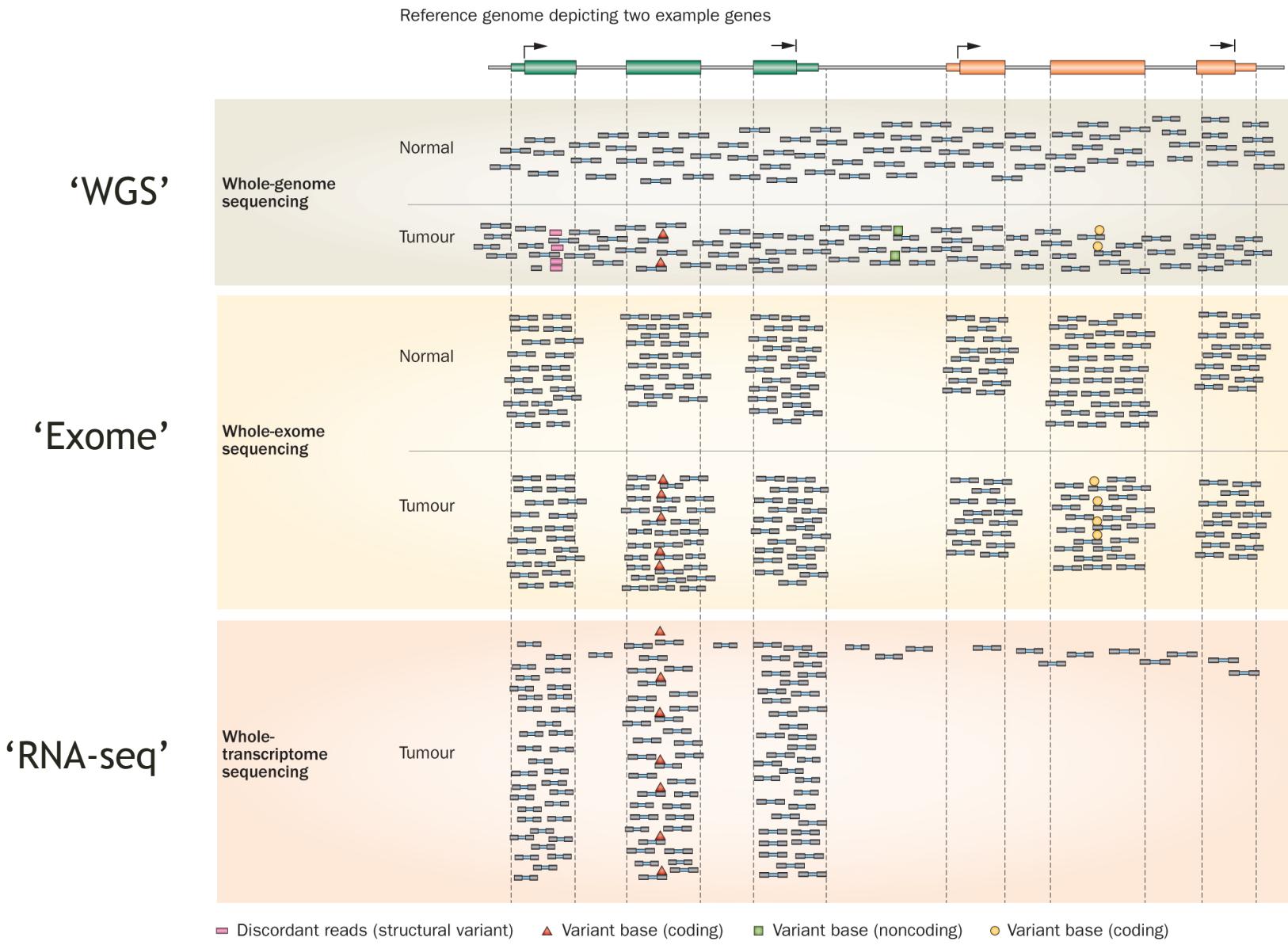
Learning objectives of module 5

- Variant annotation and interpretation
 - Types of variation
 - Key concepts for interpreting variants
 - Variant resources
 - Human disease
 - Cancer
 - Non-human
 - Functional characterization
 - Clinical relevance

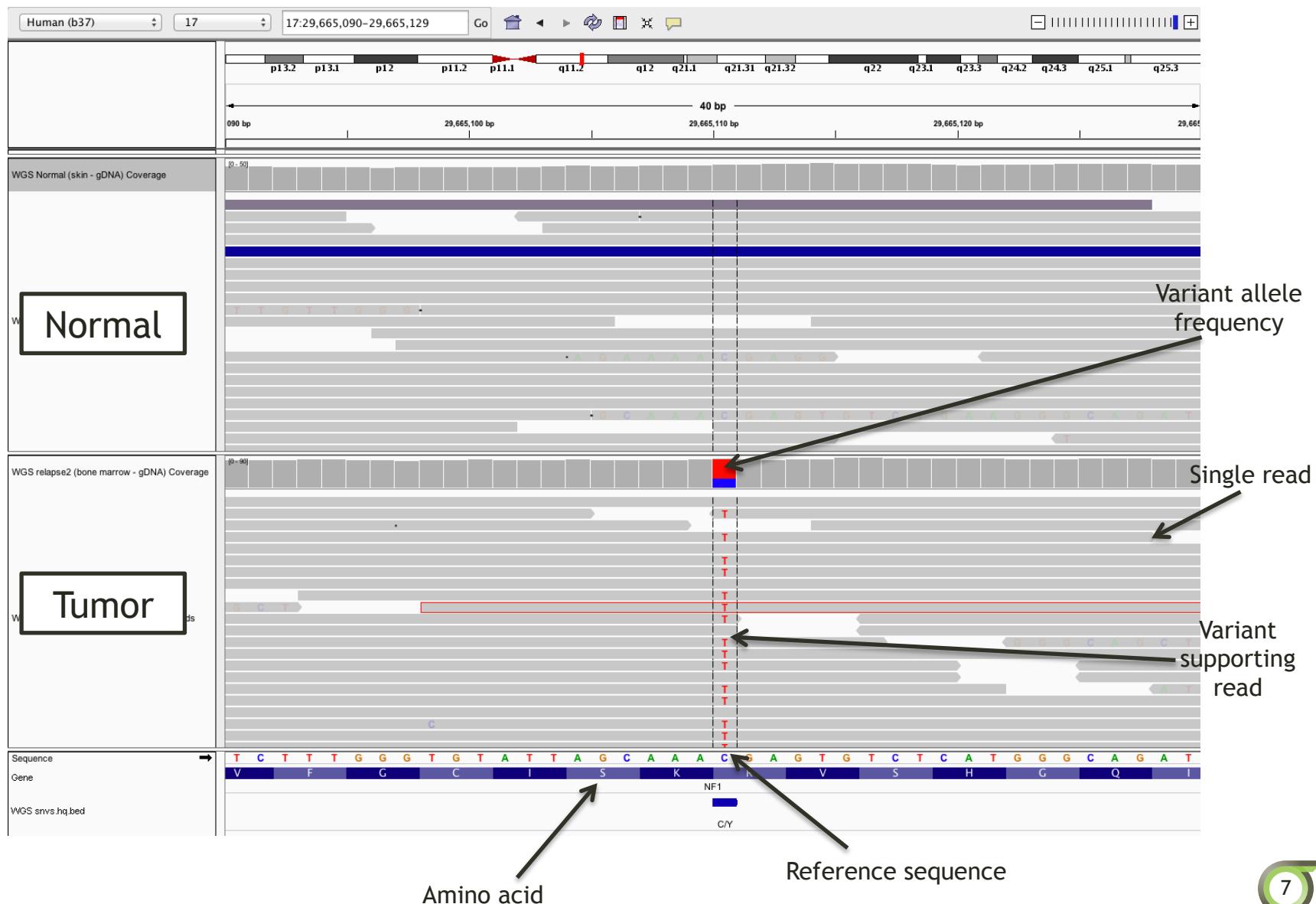
Cancer genomics research has exploded with the rapid advances in DNA sequencing technologies



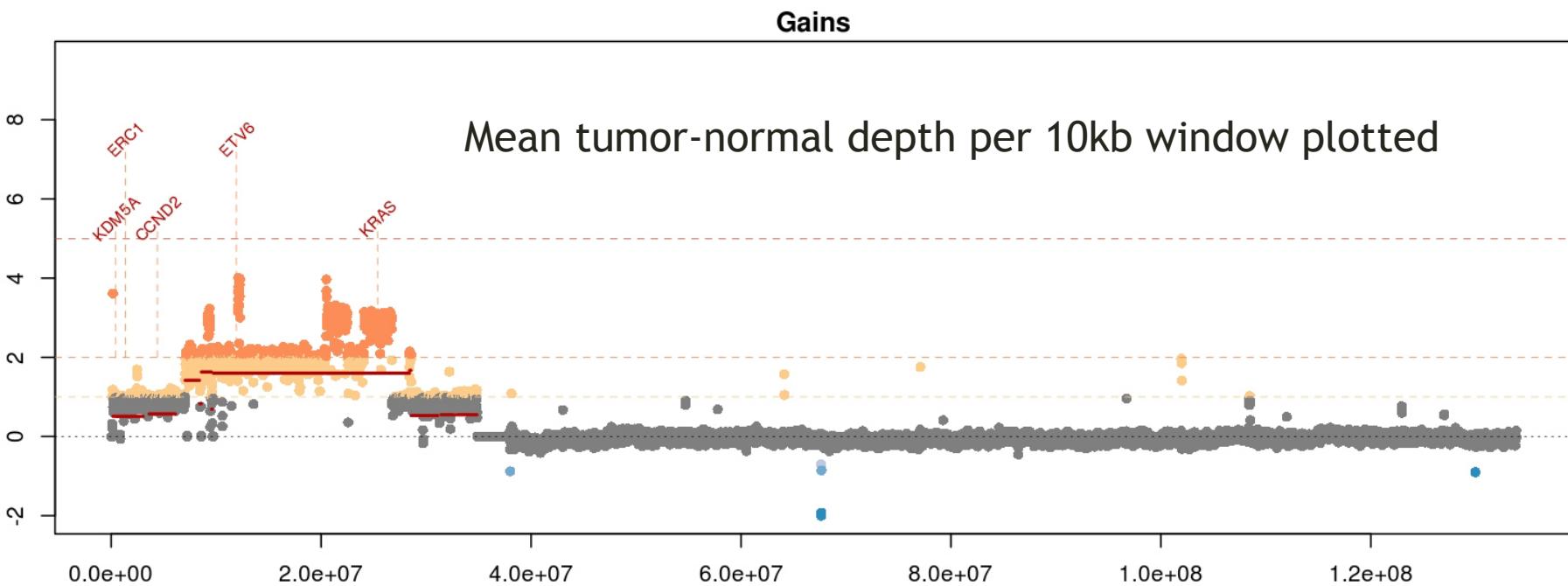
Whole genome, exome and transcriptome sequencing allows us to detect and confirm many different variant types



Single nucleotide variants (SNVs) and insertions/deletions (indels) appear as short alignment discrepancies from reference genome



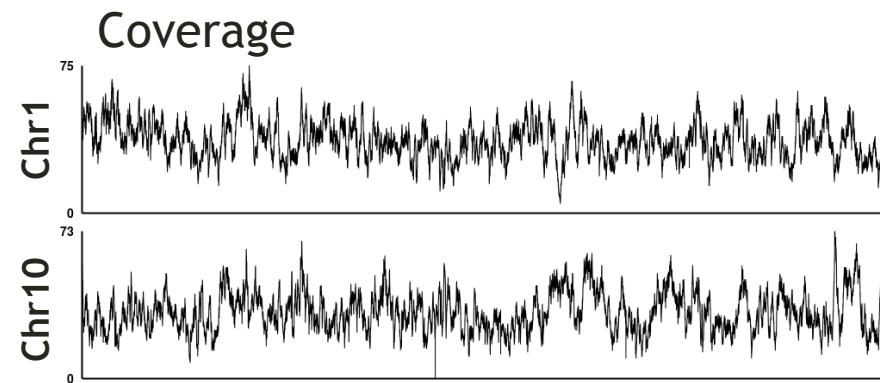
Copy number variants (CNVs) appear as deviations from in alignment “depth” or “coverage”



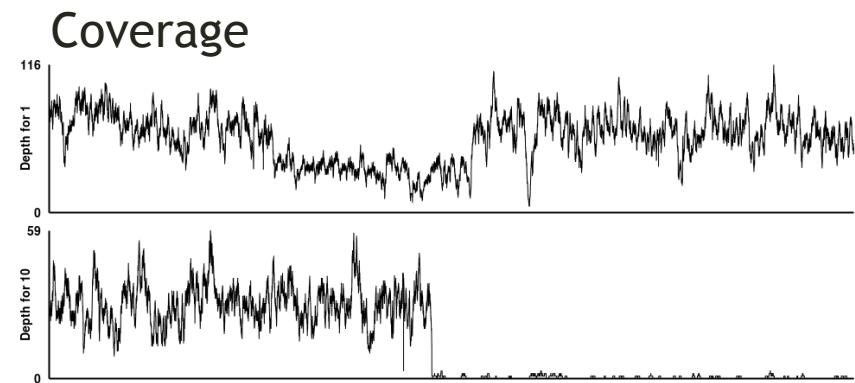
KRAS amplification in a metastatic breast cancer

Structural variants (SVs) can be identified using a combination of coverage and discordant read alignments

Normal



Tumor



Chr1

1:168243587 1:168284587

Chr10

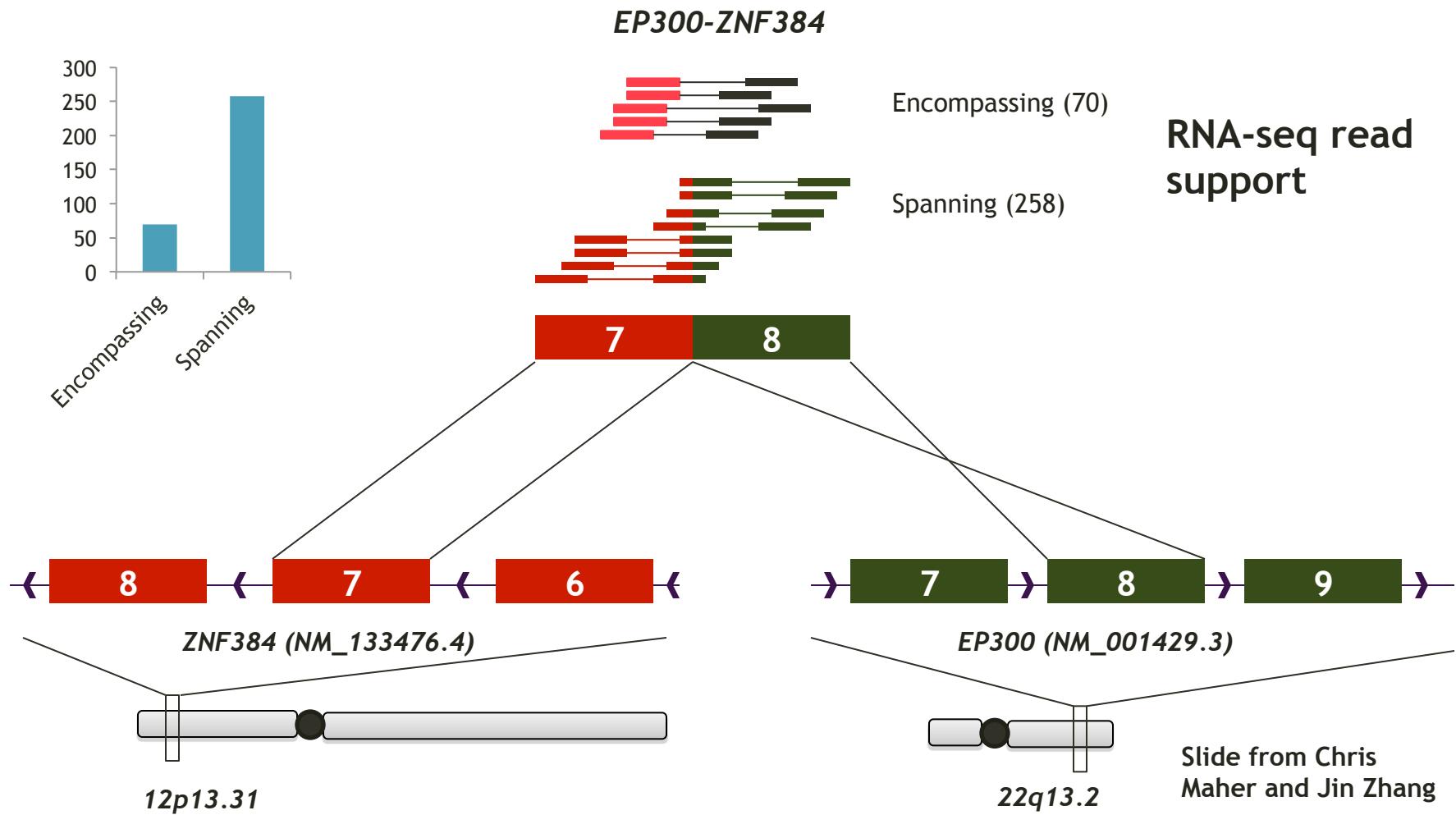
10:104273357 10:104314357 1:168243587 1:168284587

Discordant read support

A Chr1-Chr10 (TBX19-SUFU) unbalanced translocation identified in an adult acute lymphocytic leukemia.

Discordant read support

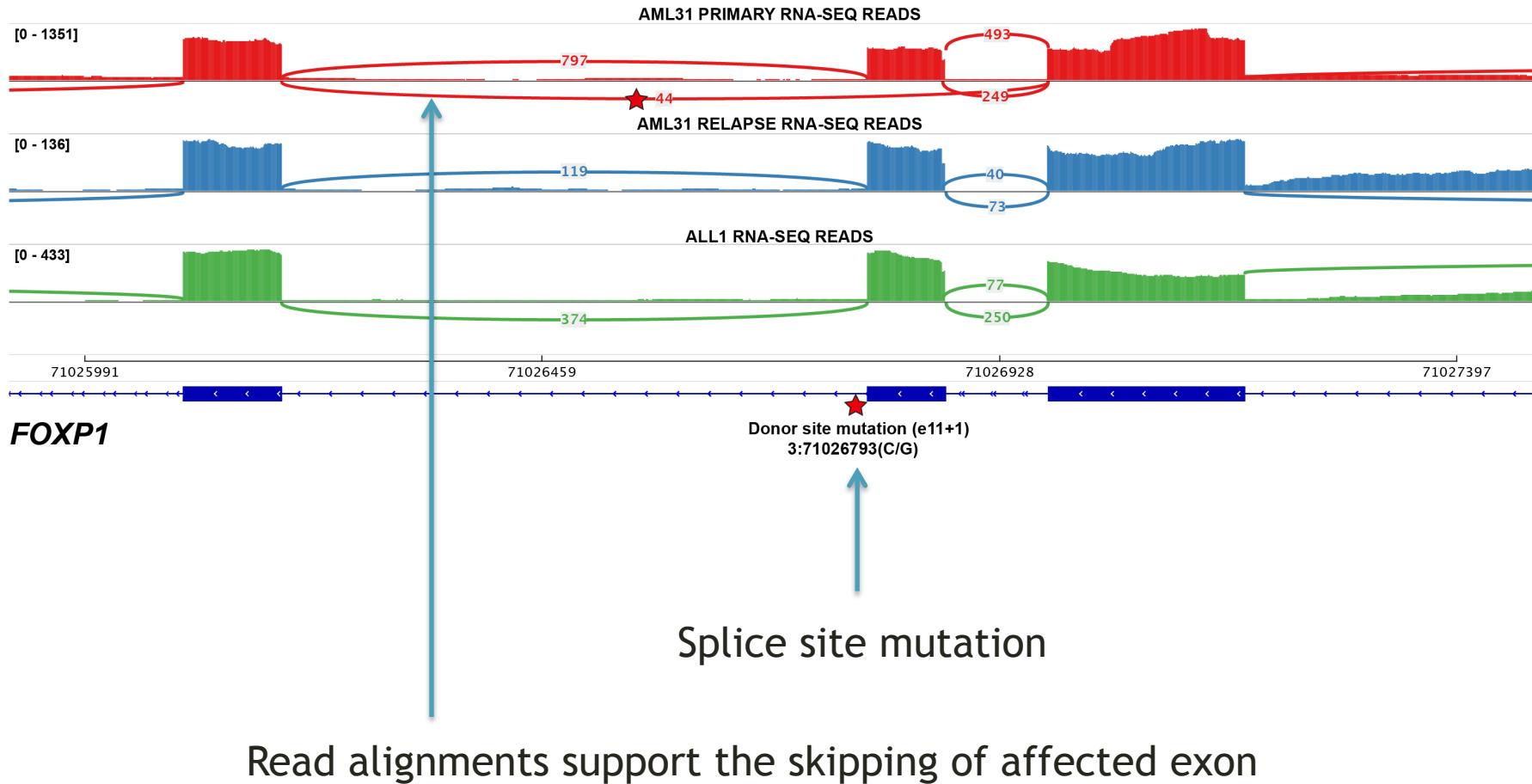
Expressed gene fusions can be identified by discordant read alignments spanning known exons from RNA-seq data



Exons 1-8 of EP300 fused to exons 7-10 of ZNF384 in head-to-tail fashion.

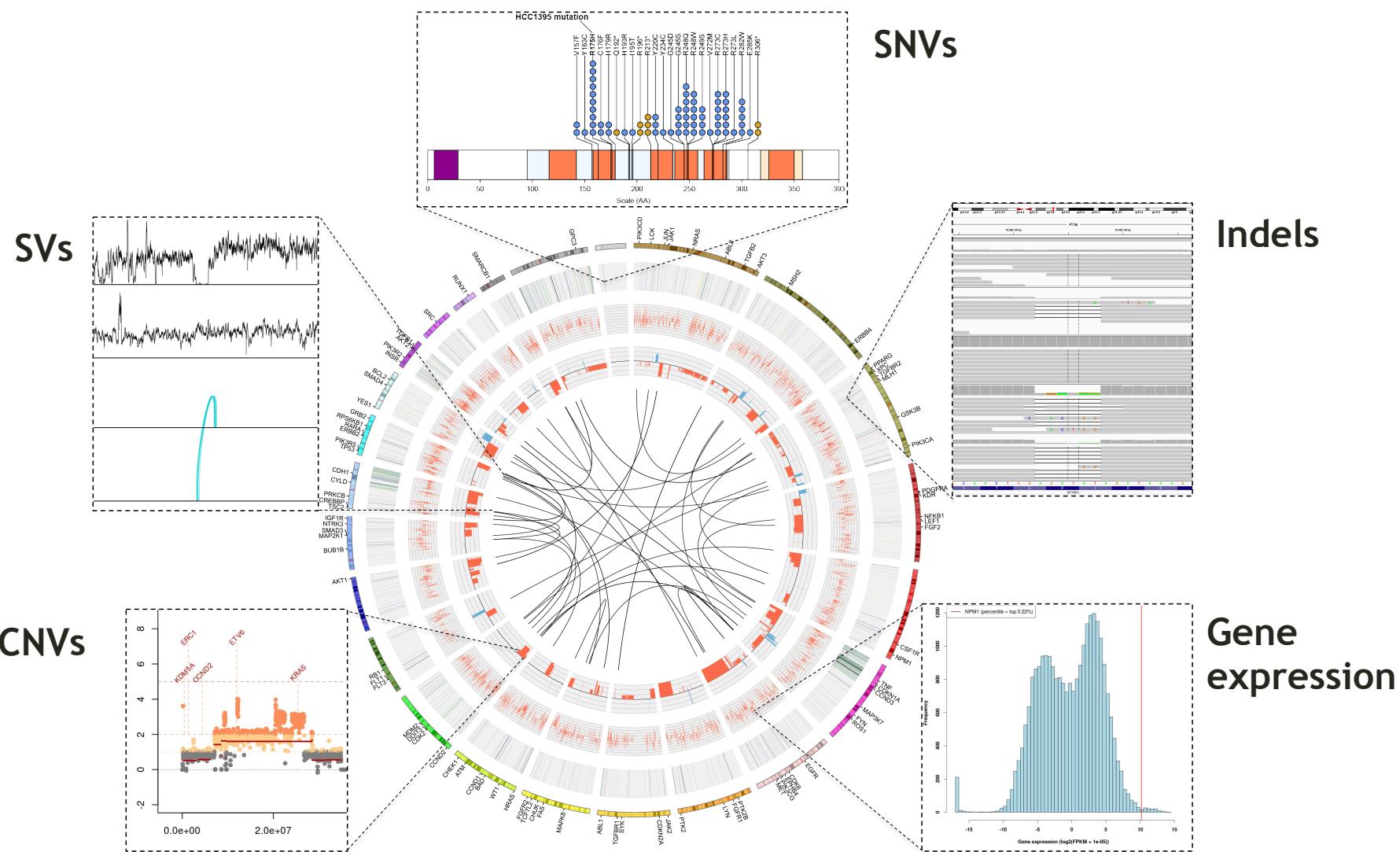
RNA-seq can also reveal the splicing consequence of somatic mutations detected in WGS

A. Sub-clonal somatic splicing event in *FOXP1* observed in the primary tumor but cleared in relapse

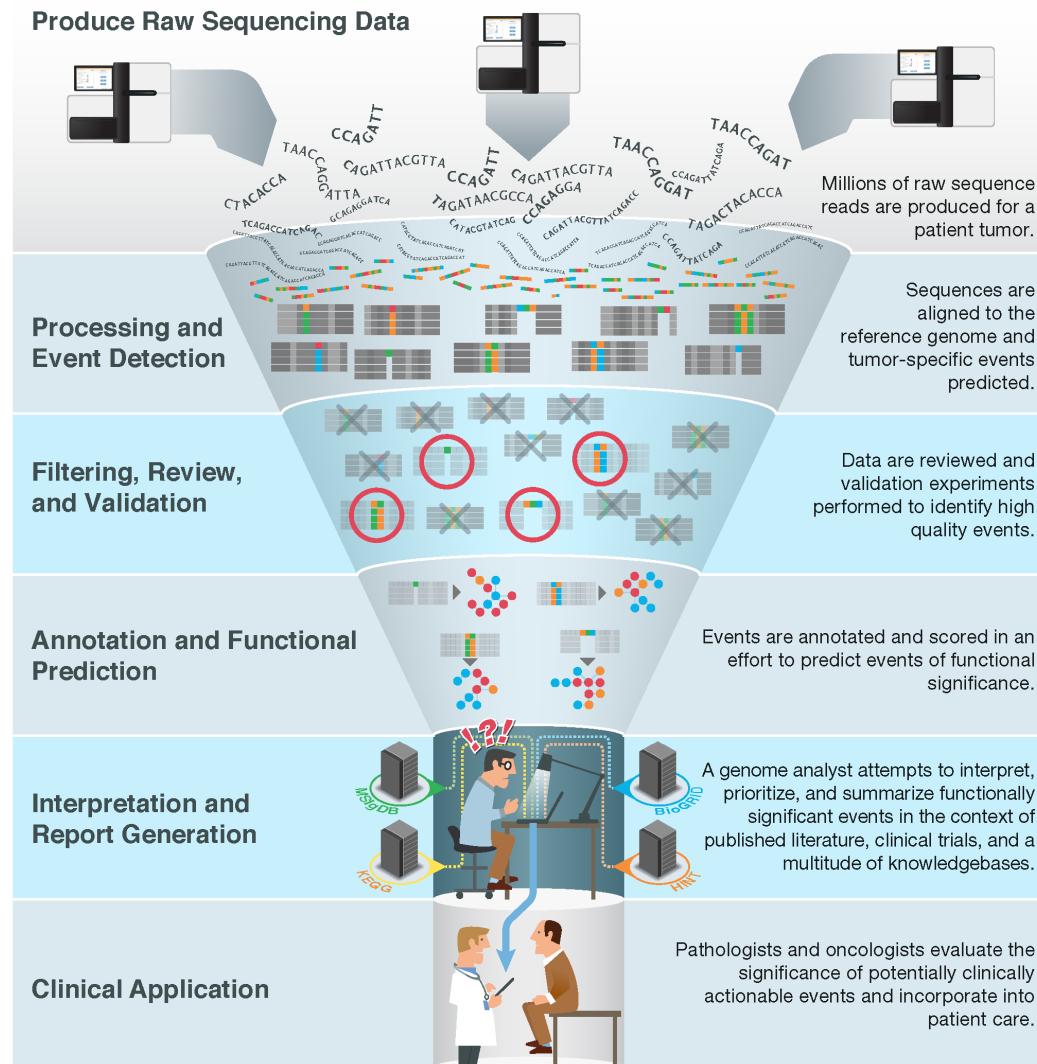


We created '[RegTools](#)' to help characterize these kinds of events

Tumor genome analysis will typically reveal dozens to thousands of alterations of multiple types

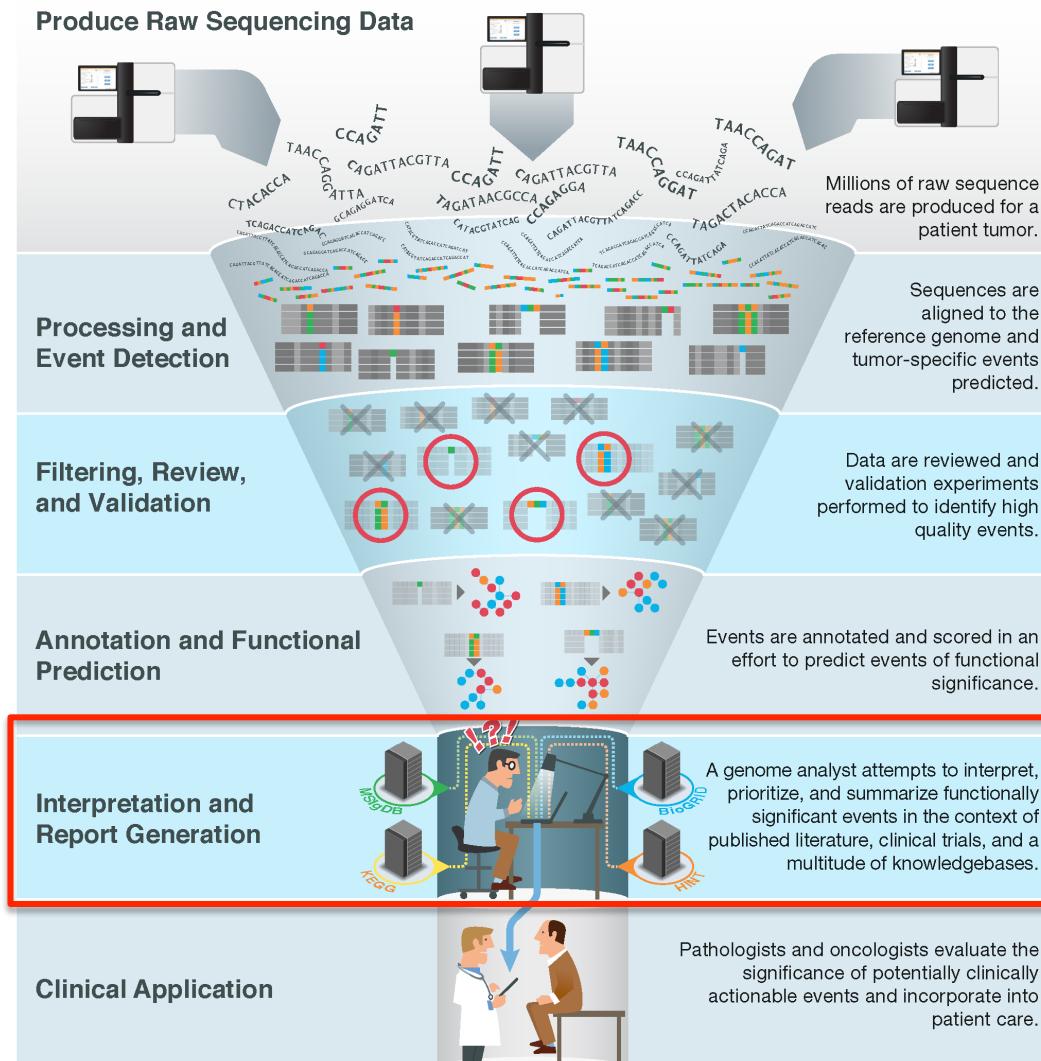


Despite remaining challenges, most aspects of sequencing and analysis have been standardized and streamlined



Good BM, Ainscough BJ, McMichael JF, Su Al†, Griffith OL†. 2014. Genome Biology. 15(8):438.

Interpretation of genomic alterations in the context of the clinical relevance remains the major bottleneck



Good BM, Ainscough BJ, McMichael JF, Su Al†, Griffith OL†. 2014. Genome Biology. 15(8):438.

Variant analysis/interpretation starts with a raw variant list (VCF file)

#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO	FORMAT	H_TU-GTB15-3685	H_TU-GTB15-M1501867	
1	1026106	.	G	T	.	PASS	NT=ref;QSS=18;QSS_NT=18;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1216591	.	G	A	.	PASS	NT=ref;QSS=120;QSS_NT=108;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1249123	.	G	T	.	PASS	NT=ref;QSS=16;QSS_NT=16;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1262394	.	G	T	.	PASS	NT=ref;QSS=34;QSS_NT=34;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1326886	.	C	T	.	PASS	NT=ref;QSS=199;QSS_NT=157;SGT=CC->CT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1391597	.	T	C	.	PASS	NT=ref;QSS=32;QSS_NT=32;SGT=TT->CT;TQSS=2;TQSS_NT=2			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1904481	.	G	T	.	PASS	NT=ref;QSS=24;QSS_NT=24;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1912142	.	G	T	.	PASS	NT=ref;QSS=33;QSS_NT=33;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	1919717	.	G	A	.	PASS	NT=ref;QSS=17;QSS_NT=17;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	2319028	.	C	T	.	PASS	NT=ref;QSS=76;QSS_NT=76;SGT=CC->CT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	2333646	.	G	T	.	PASS	NT=ref;QSS=26;QSS_NT=26;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	3328555	.	G	T	.	PASS	NT=ref;QSS=20;QSS_NT=20;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	3350384	.	G	A	.	PASS	NT=ref;QSS=33;QSS_NT=33;SGT=GG->AG;TQSS=2;TQSS_NT=2			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	3388456	.	C	T	.	PASS	NT=ref;QSS=55;QSS_NT=55;SGT=CC->CT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	3662615	.	G	T	.	PASS	NT=ref;QSS=18;QSS_NT=18;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	3774072	.	G	T	.	PASS	NT=ref;QSS=21;QSS_NT=21;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	6021727	.	G	A	.	PASS	NT=ref;QSS=16;QSS_NT=16;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	6271112	.	G	T	.	PASS	NT=ref;QSS=52;QSS_NT=52;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	6278217	.	G	T	.	PASS	NT=ref;QSS=30;QSS_NT=30;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	6609812	.	G	A	.	PASS	NT=ref;QSS=74;QSS_NT=74;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	9338624	.	G	A	.	PASS	NT=ref;QSS=15;QSS_NT=15;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	10678477	.	G	T	.	PASS	NT=ref;QSS=26;QSS_NT=26;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	10720178	.	G	T	.	PASS	NT=ref;QSS=33;QSS_NT=33;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11140620	.	A	C	.	PASS	NT=ref;QSS=20;QSS_NT=20;SGT=AA->AC;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11194363	.	G	T	.	PASS	NT=ref;QSS=19;QSS_NT=19;SGT=GG->GT;TQSS=2;TQSS_NT=2			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11294450	.	C	T	.	PASS	NT=ref;QSS=35;QSS_NT=35;SGT=CC->CT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11561899	.	G	A	.	PASS	NT=ref;QSS=32;QSS_NT=32;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11595041	.	G	A	.	PASS	NT=ref;QSS=137;QSS_NT=105;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11735264	.	G	T	.	PASS	NT=ref;QSS=170;QSS_NT=122;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11852226	.	G	T	.	PASS	NT=ref;QSS=39;QSS_NT=39;SGT=GG->GT;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	11855448	.	G	A	.	PASS	NT=ref;QSS=32;QSS_NT=32;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	
1	12198424	.	G	A	.	PASS	NT=ref;QSS=24;QSS_NT=24;SGT=GG->AG;TQSS=1;TQSS_NT=1			GT:AD:BQ:SS:DP:FDP:SDP:SUBDP:AU:CU:GU: TU:FT	

Details of the VCF file format: [hts-specs](#), [VCF-v4.2.pdf](#)

How do we interpret these variants?

Important concepts in the interpretation of variants

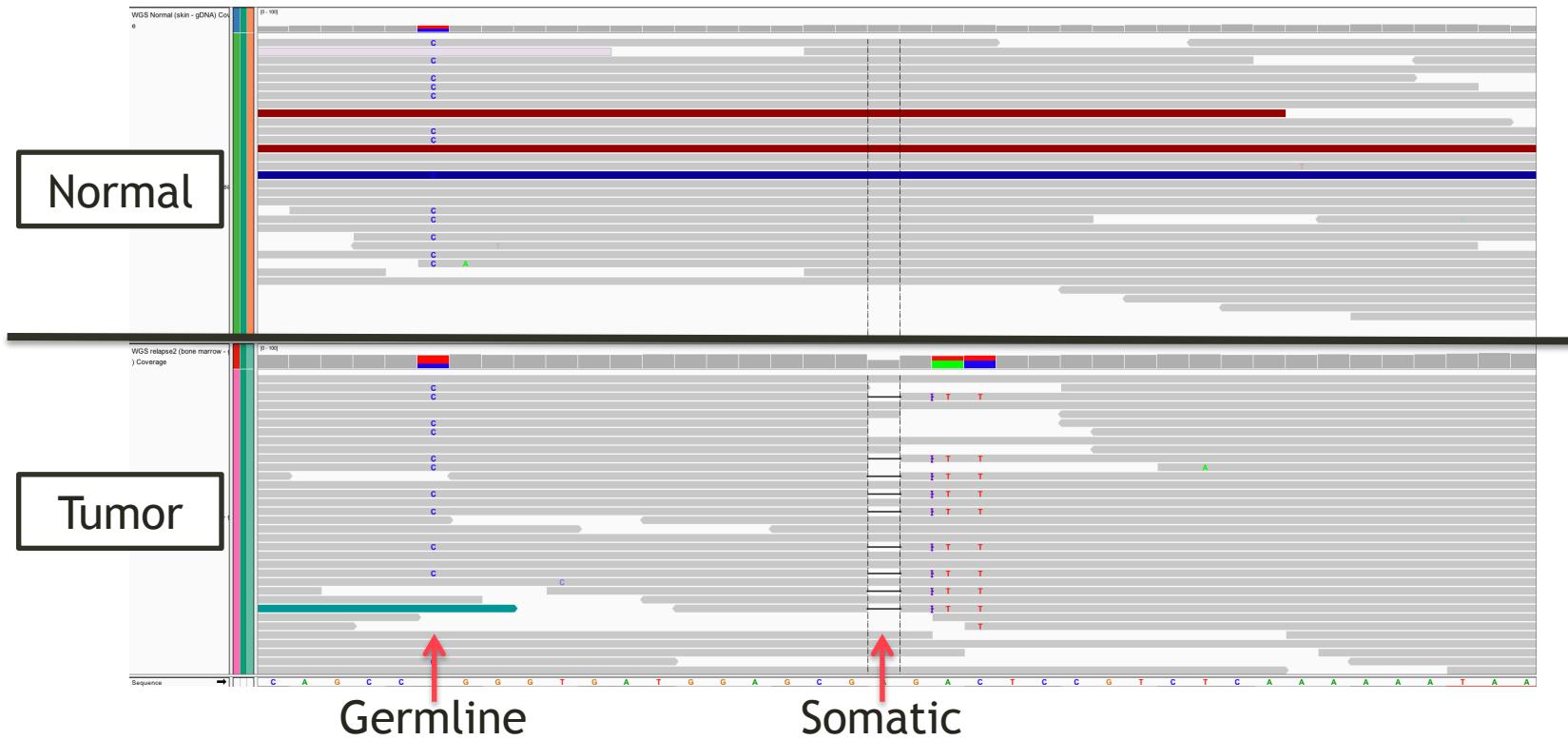
- False positives vs. true positives
- Somatic mutation vs. germline mutation vs. germline polymorphism
- Gain-of-function (activating) vs. loss-of-function (inactivating)
- Deleterious vs. tolerated
- Recurrent vs. random
- Driver vs. passenger
- Dominant clone vs. sub-clonal
- Regulatory vs. coding
- Relevant to cancer biology
 - ‘canonical’ variants, ‘hotspot’ variants, ‘cancer genes’
- Clinically relevant / ‘actionable’
 - ‘Druggable’
 - Predictive, prognostic, diagnostic, predisposing

Somatic mutation vs. germline mutation vs. germline polymorphism

- Somatic mutations are best distinguished by adequate sequencing of a matched normal
 - Affected and unaffected family members may help to determine origin of a germline mutation
- Comparison of variants to variant databases can also help to classify variants as:
 - Germline polymorphisms
 - [1000 genomes](#)
 - [Exome sequencing project](#) (~6,500 individuals)
 - [ExAC, Exome Aggregation Consortium](#) (~60,000 individuals)
 - [gnomAD browser](#) (123,136 WXS and 15,496 WGS)
 - Germline mutations
 - [OMIM](#), [HGMD](#), [PharmGKB](#), [ClinVar](#)
 - [ACMG guidelines](#)
 - [Gemini](#)
 - Somatic mutations
 - By inference if the mutation is not a common polymorphism (often a weak inference) or is a classic hotspot mutation

Somatic versus germline demonstration

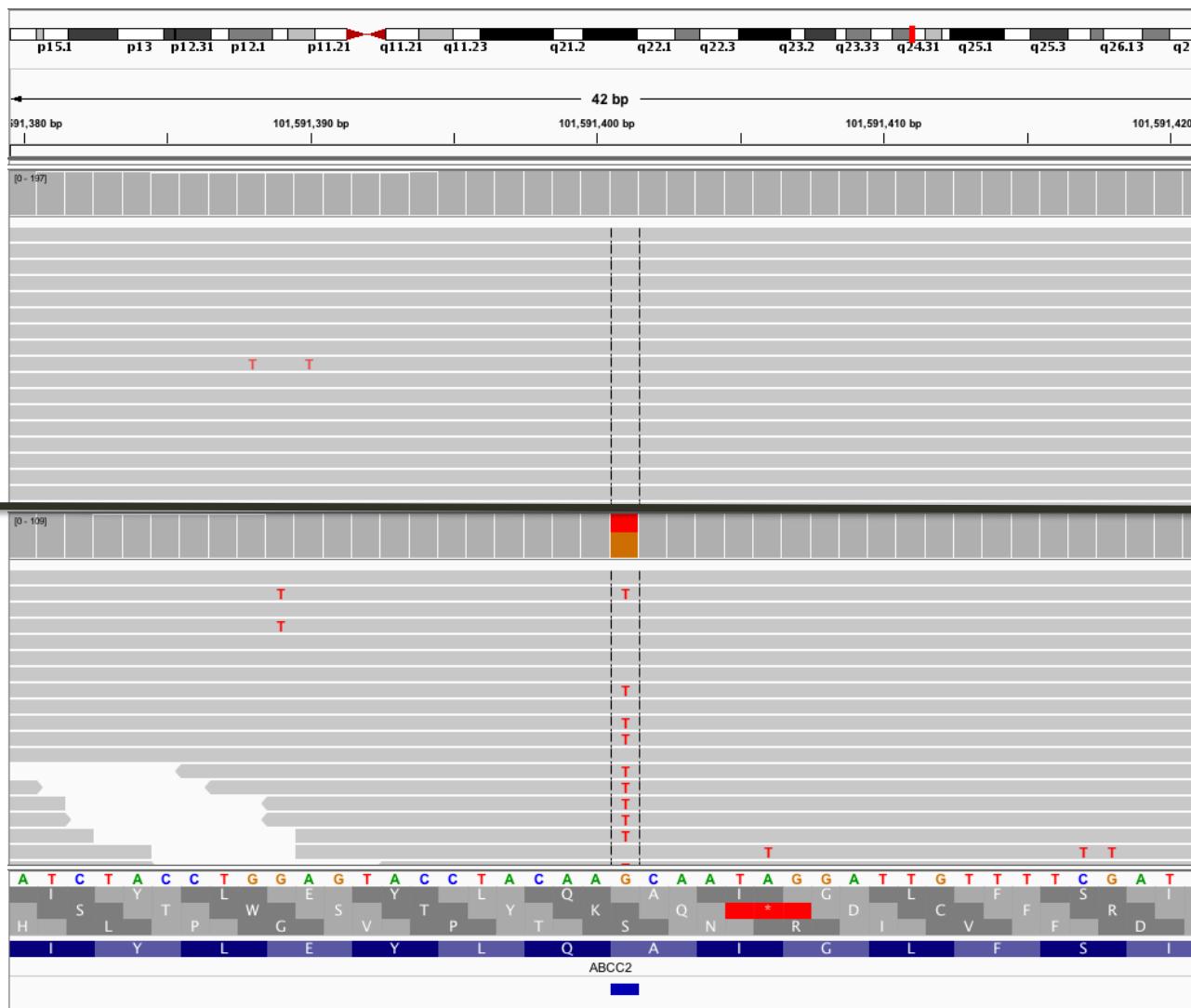
- Germline mutations
 - Present in egg or sperm
 - All cells of affected offspring
 - Heritable
 - Cause of familial cancers
- Somatic mutations
 - Occur in non-germline tissues
 - Only tumor cells (breast, lung, blood, etc.)
 - Non-heritable
 - Cause of sporadic cancers



False positives

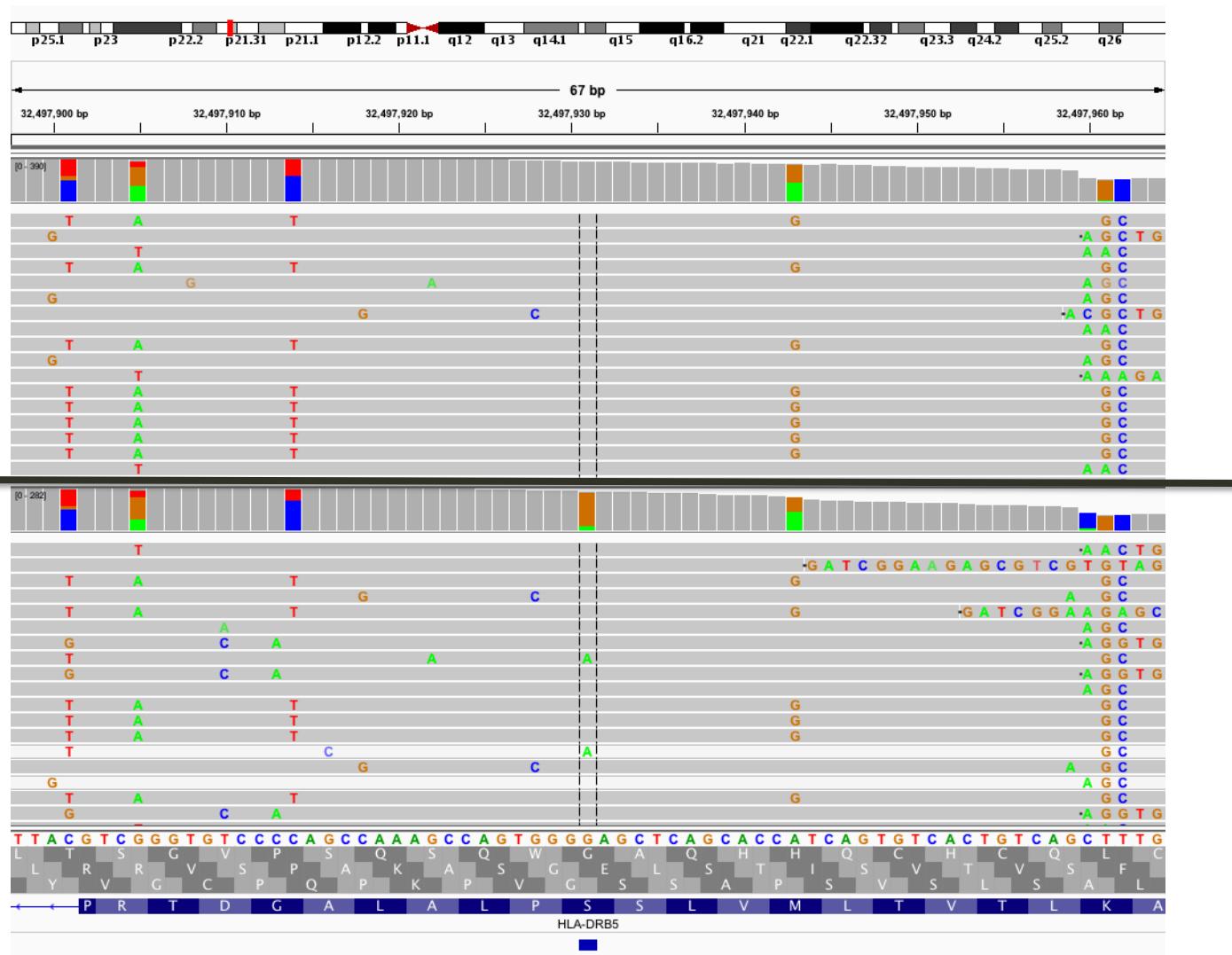
- Use IGV to examine alignments for artifacts
 - Use an intersection of variant callers
 - “panel of normals” analysis
-
- Useful resources
 - [Discussion of variant callers](#)
 - [Optimizing tumor genome analysis](#)
 - [Hands-on IGV tutorial](#)

Example of a high quality somatic variant



This G/T variant was independently called by 5 somatic variant callers

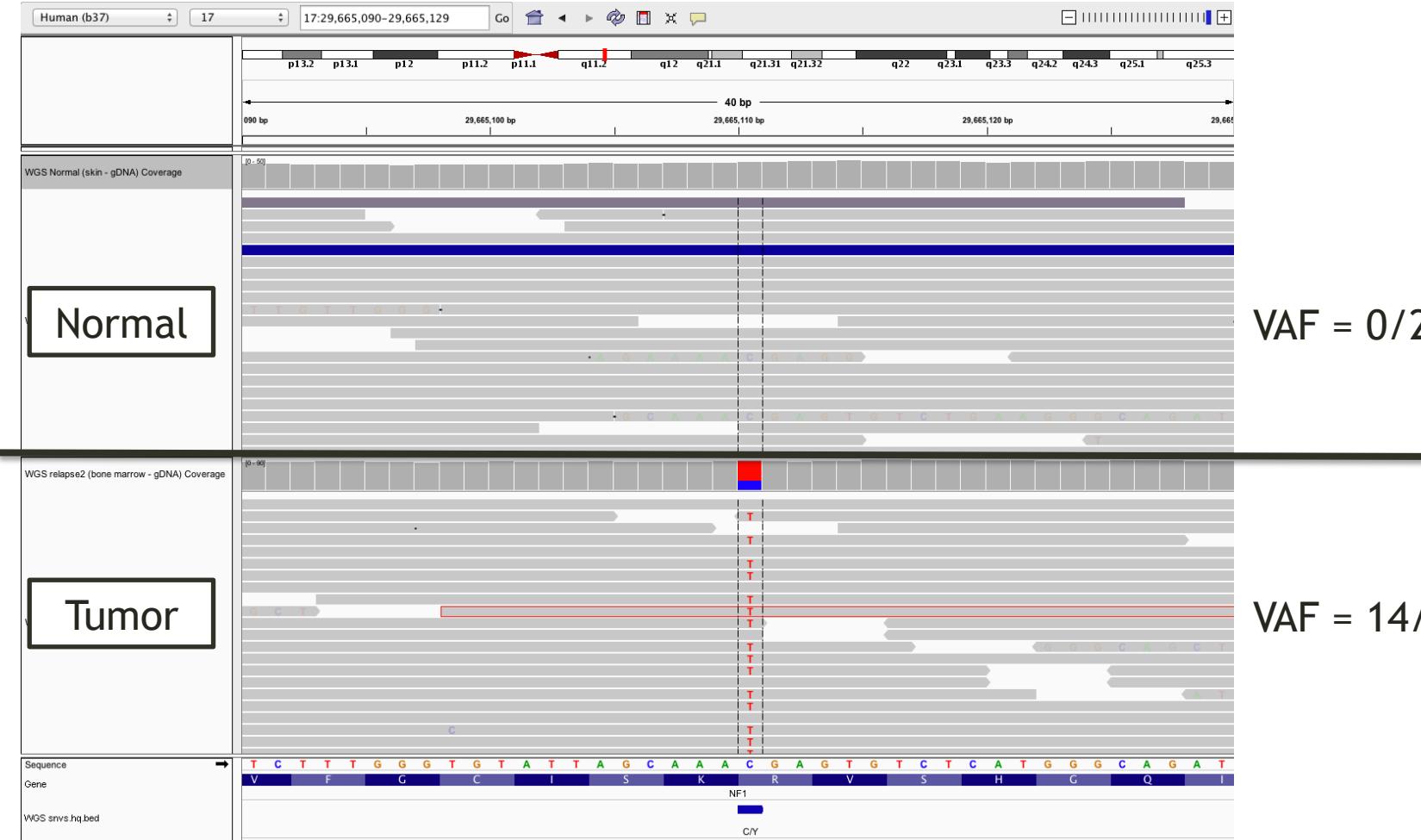
Example of a low quality somatic variant



This G/A variant was called by only 1 of 5 somatic variant callers

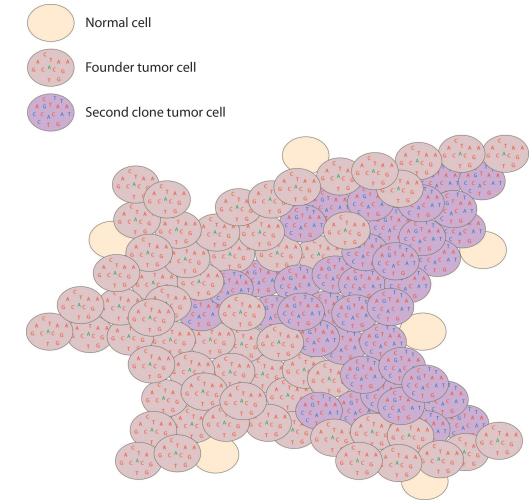
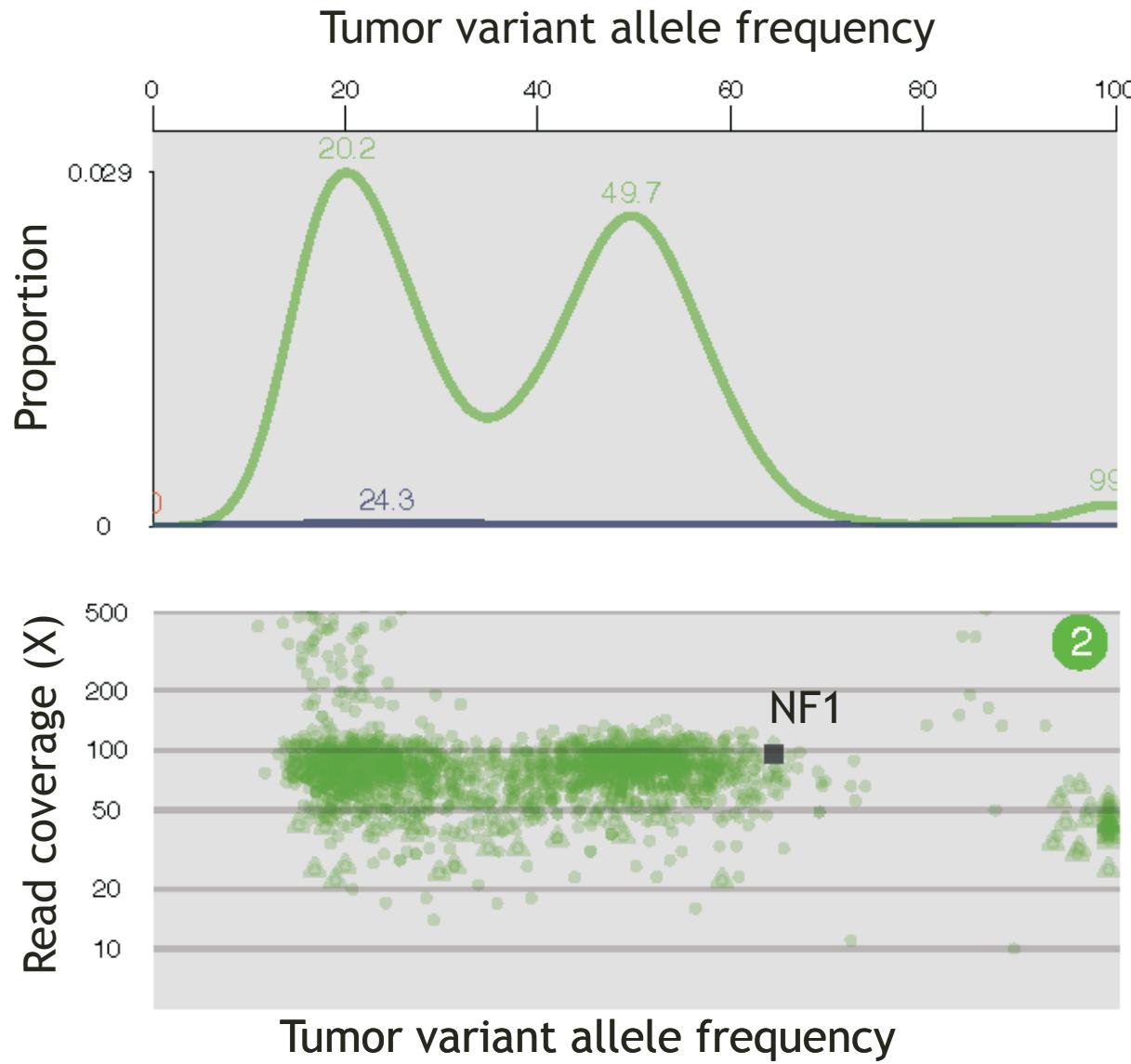
Variant allele frequency (VAF)

VAF = Variant reads / Total reads



A heterozygous variant is expected to have VAF = 50%. Often not true due to sample purity, tumor heterogeneity, sampling error, alignment issues, copy number variation, etc.

Dominant clone vs. sub-clonal (and driver vs. passenger)

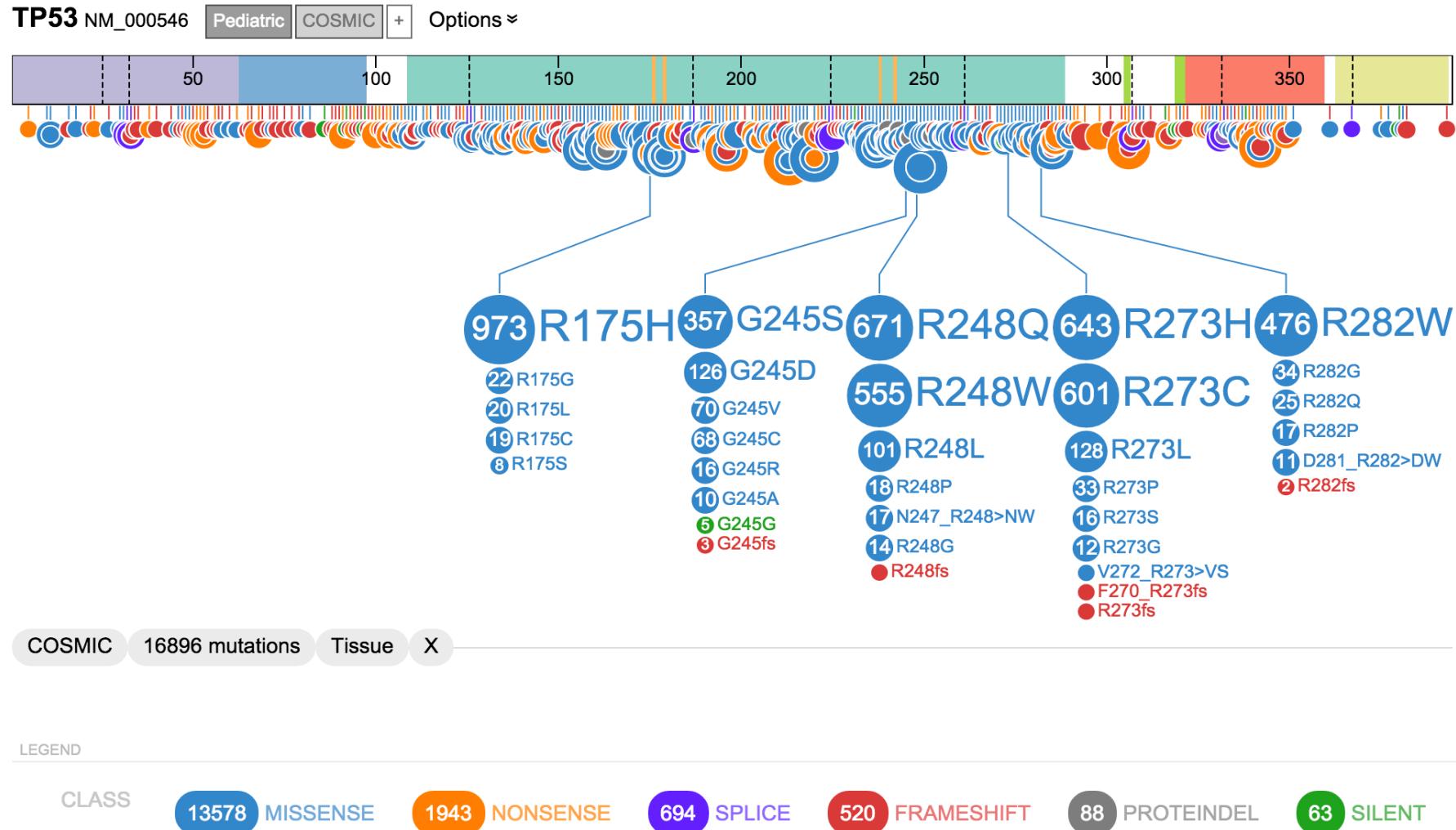


WGS data

Gain-of-function vs. Loss-of-function

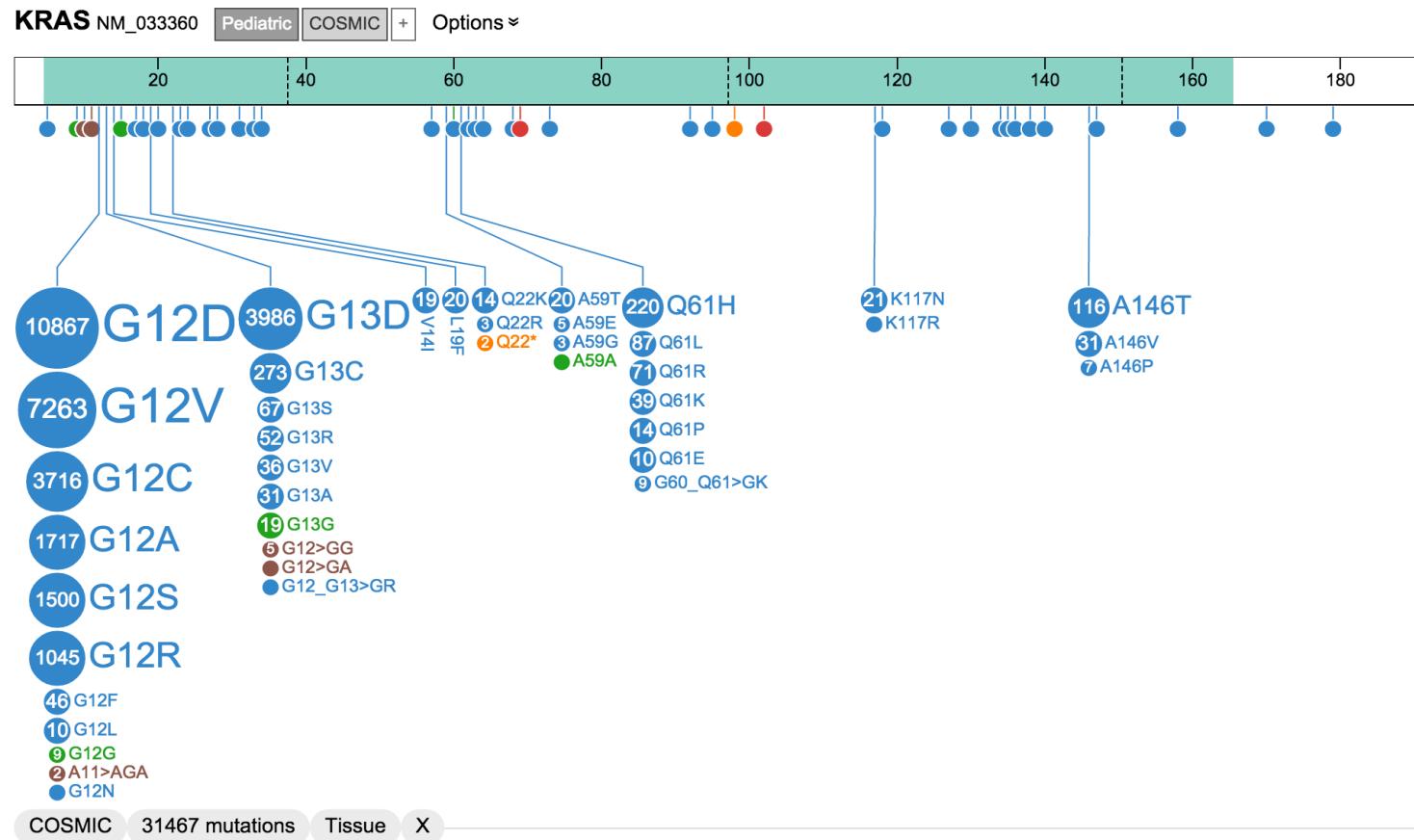
- Gain-of-function and loss-of-function generally refer to a change in specific function of a gene product (protein or RNA) leading to a phenotypic effect
 - Loss-of-function implies that a normal gene function is no longer possible
 - Many random mutations can lead to inactivation
 - Manifests in mutation data as scattered across the length of the gene and may be frameshift, nonsense, and splice site mutations
 - Gain-of-function implies an increased or new gene function
 - There are far fewer ways to create an activating mutation
 - These tend to have dominant phenotypes
 - Manifest in mutation data as “hotspots”
 - Usually missense mutations
- The pattern of ***recurrence*** can be a powerful hint for distinguishing activating vs. inactivating mutations.

Gain-of-function vs. Loss-of-function



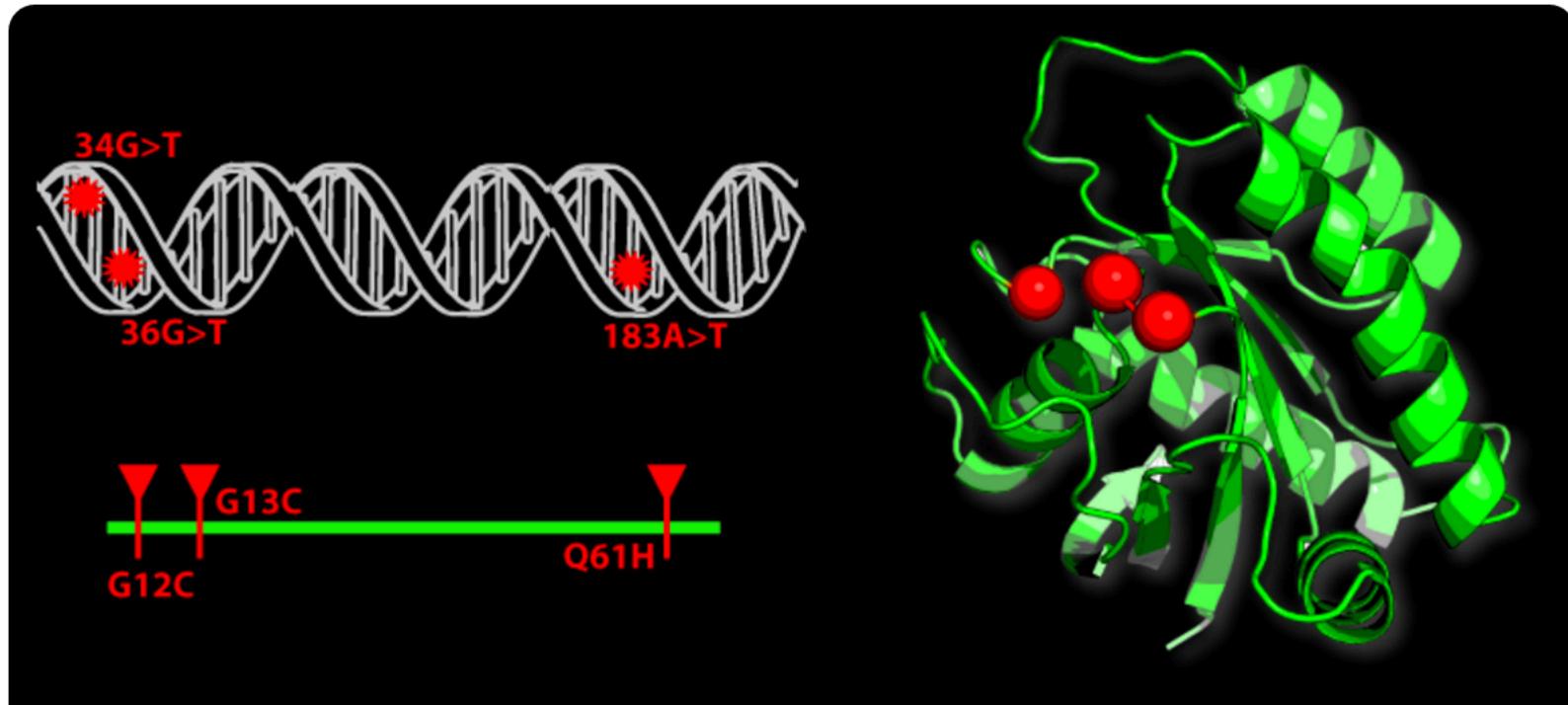
TP53: Recurrence pattern and mutation types suggest loss-of-function

Gain-of-function vs. Loss-of-function



KRAS: Recurrence pattern and mutation types suggest gain-of-function

Gain-of-function “hotspots” may be missed in 2D but seen in 3D models of protein structure



From: [Mutation3D](#) website.

For a more detailed discussion of relevant tools:

[Finding Mutation Hotspot At Level Of Amino Acid By Spatial Proximity In Protein Structures](#)

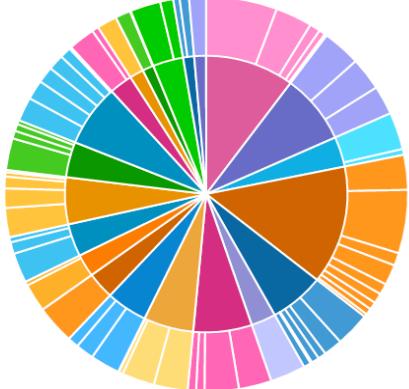
Recurrent vs. random/background mutation

- Recurrent mutation of a gene or pathway can imply functional relevance of that gene/pathway
- Particular somatic mutations that are recurrent (e.g. BRAF V600E) can imply an activating mutation
- One of the most basic (but fruitful) goals of large scale tumor genome sequencing projects has been to look for these patterns of recurrence
 - Since random/background mutation rates can be very high in some tumors, determining whether an observed level/pattern of recurrence is **significant** is important
 - Overall mutation burden, gene size, pathway size, systematic artifacts, and other factors complicate this goal

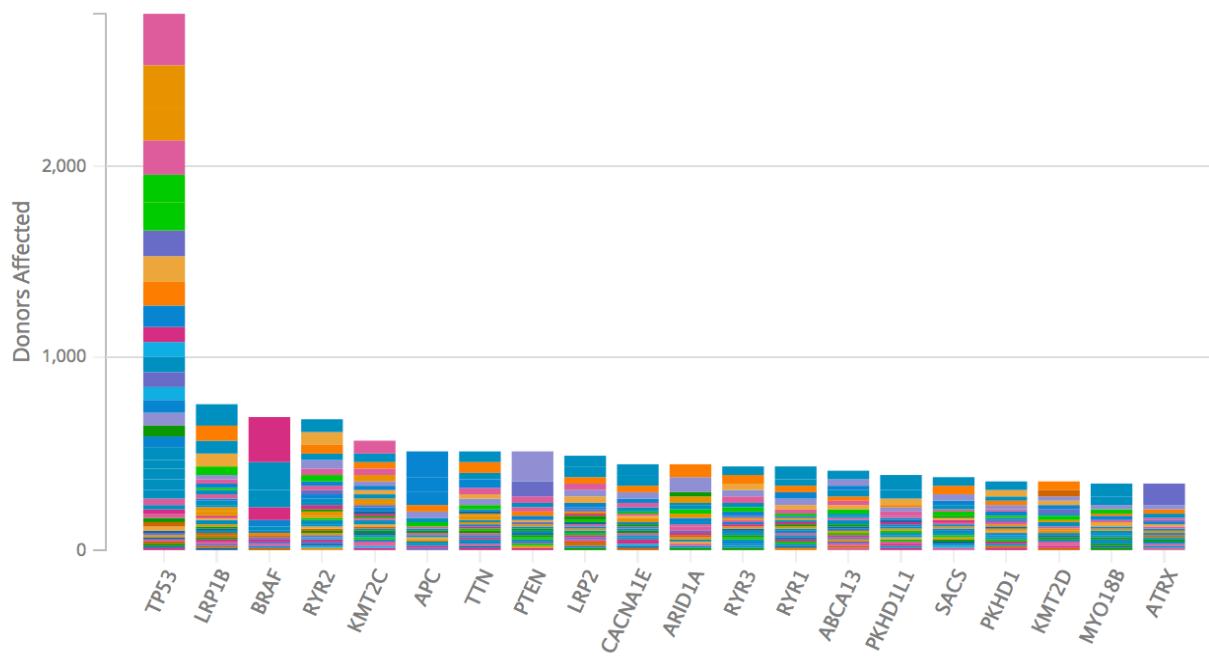
Human disease variation resources and initiatives

Cancer variation resources: TCGA and ICGC have sequenced 10,000s of exomes, 1,000s of whole genomes

Donor Distribution
19,305 Donors across 70 Projects



Top 20 Mutated Genes with High Functional Impact SSMs
10,648 Unique SSM-Tested Donors



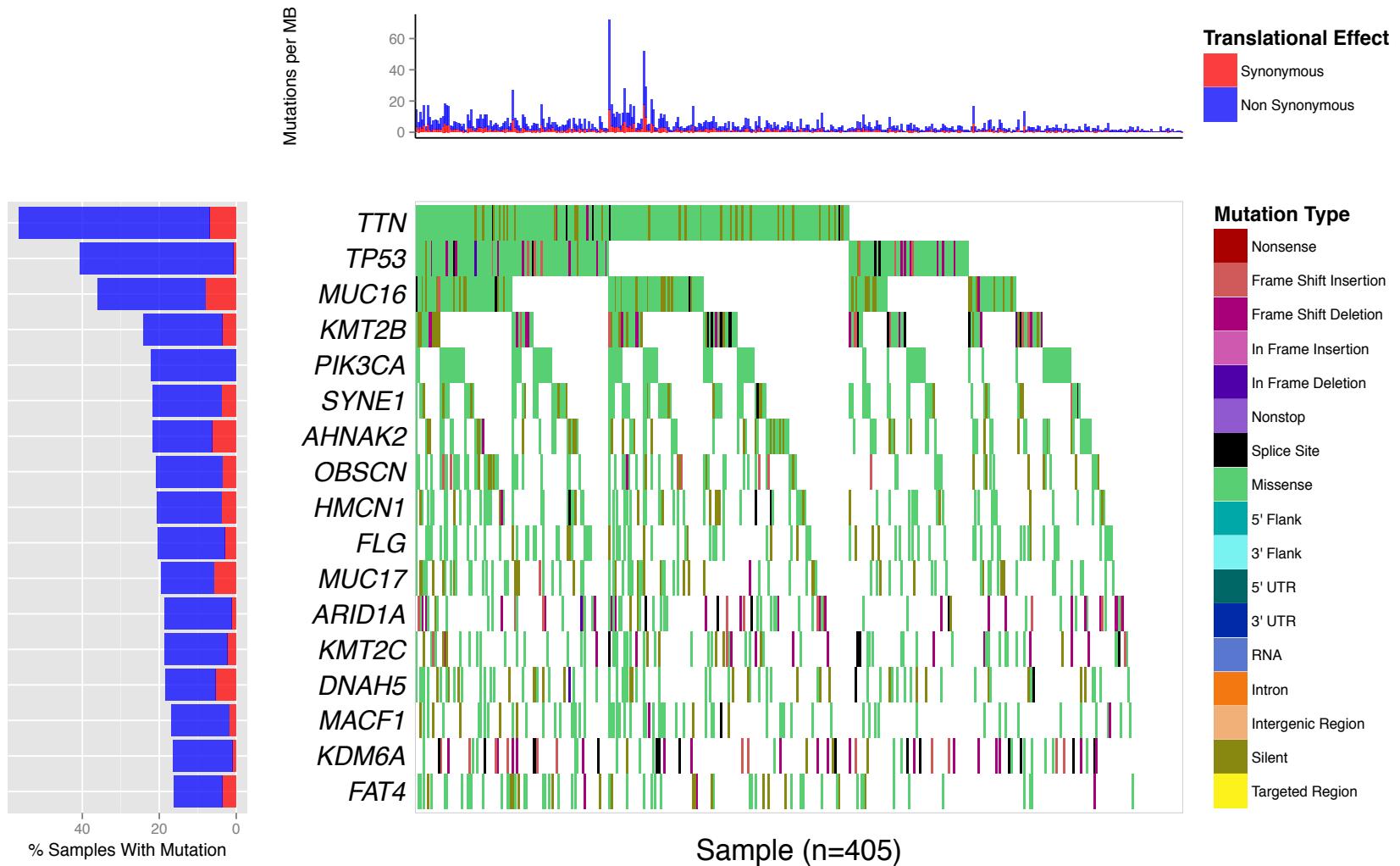
<https://dcc.icgc.org/>

Exploring cancer mutation data portals

- Many, many resources
- Some of the resources that we find most useful
 - [Genomic data commons](#)
 - [ICGC data portal](#)
 - [cBioPortal](#) ([OncoPrinter](#) & [MutationMapper](#))
 - [Cosmic](#)
 - [TCGA data portal](#)
 - [St. Jude pediatric cancer portal](#) ([ProteinPaint](#))
- We track (blog about) these resources as they develop (on BioStars [here](#)).

Non-human variation resources

A ‘waterfall’ plot is one way to visualize the pattern of recurrence in a cohort



<https://github.com/griffithlab/GenVisR>

Deleterious vs. tolerated (functional vs. non-functional)

- Many tools/resources attempt to classify variants as “deleterious” vs. “tolerated” (aka “benign”)
 - E.g. Sift, PolyPhen, Condel, [CADD](#), etc.
- The goal of these tools is often confused with predicting whether the mutation is gain-of-function/activating
 - Not the same thing...
 - Mostly driven by sequence conservation (though CADD considers a more complex set of features)
- Variant effect annotators
 - VEP, snpEff, ANNOVAR, VAAST

Functional relevance to cancer biology?

- Many useful resources that are gene centric
 - [Databases of tumor suppressors and oncogenes](#)
 - If the gene where a variant occurs is relevant to a disease or phenotype, then we turn our attention to the significance of the specific variant
- Does the variant have established functional relevance?
 - [DoCM - the Database of Curated Mutations](#) is a resource that aggregates specific variants with documented relevance to cancer
 - **Others**

Clinically relevant?

- A gene or variant can be relevant to disease biology or a specific phenotype but not have any established clinical relevance
 - Arguably this is mostly the case...
 - The majority of genes and variants when observed do not lead to a clinical action
- Types of clinical relevance
 - Predictive (“druggable”)
 - Prognostic
 - Diagnostic
 - Predisposing

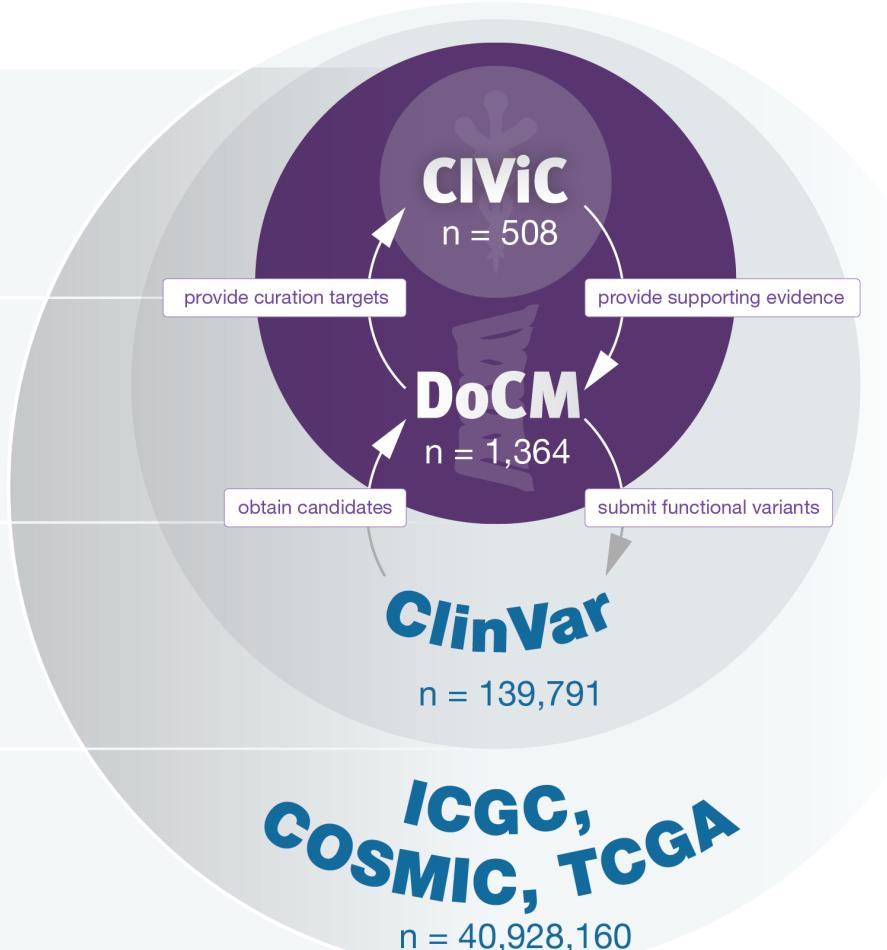
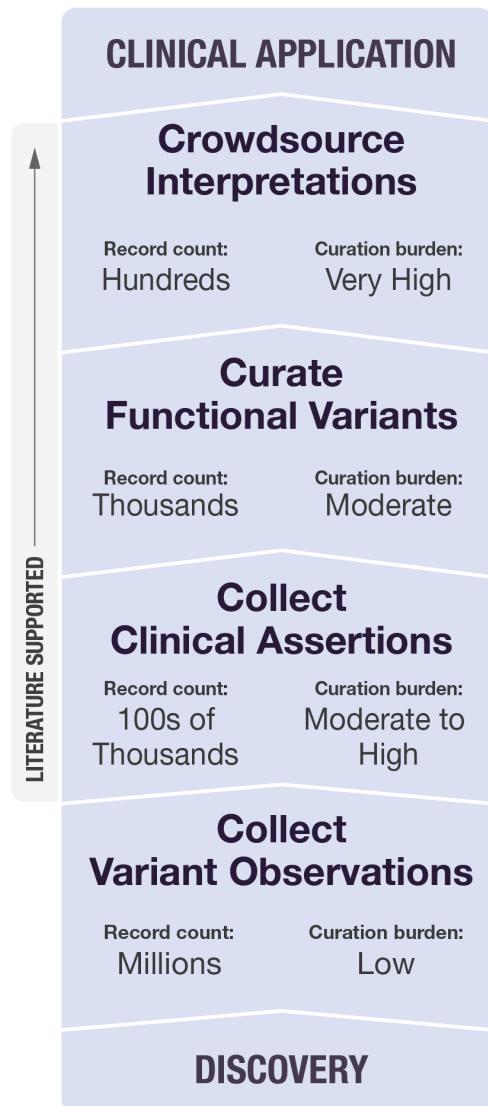
Providing current and comprehensive interpretations of clinical significance of variants is a non-trivial task

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
● PIK3CA H1047R	Mutations in PIK3CA have been reported in 26% to 33% of breast cancer cases (COSMIC, Jun 2012 and Kalinsky et al., 2009; 19671852). Activating mutations in PIK3CA, such as the one seen here, may predict sensitivity to inhibitors of PI3 kinase or its downstream signaling pathway (the PI3K/Akt/mTOR pathway) (Huang et al., 2007; 18079394). The mTOR inhibitors temsirolimus and everolimus have been tested in several clinical trials in breast cancer, and have been approved by the FDA for use in other tumor types. Inhibitors of PI3K and Akt are currently in clinical trials in breast cancer, alone or in combination with other therapies. PIK3CA mutations may play a role in resistance to hormonal therapy in ER+ breast cancers (Miller et al., 2011; 22114931). Activating mutations in PIK3CA may also confer resistance to anti-Her2 therapies (Chakrabarty et al., 2010; 20581867, Kataoka et al., 2010; 19633047, Wang et al., 2011; 21676217); combined inhibition of Her2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation, though this remains an area of active investigation.
● CCND1 amplification	CCND1 amplification has been reported in approximately 10-15% of invasive breast cancers, more frequently in BRCA-negative cancers (Elsheikh et al., 2008; 17653856, Bane et al., 2011; 21327470). There are no approved therapies that directly target the protein product of CCND1 (Cyclin D1); however, CCND1 amplification may predict sensitivity to inhibitors of Cdk4 and Cdk6, which are currently under investigation in clinical trials. Overexpression of Cyclin D1 has also been associated with resistance to endocrine therapy in breast cancer (reviewed in Lange et al., 2011; 21613412; Musgrove and Sutherland, 2009; 19701242, Butt et al., 2005; 16113099).
● CDH1 E167*	CDH1 mutations are present in approximately 17% of breast cancers, and more often in luminal type cancers (COSMIC, Jun 2012, Hollestelle et al., 2010; 19593635). Loss of the E-cadherin protein, which is encoded by the CDH1 gene, has been associated with poor prognosis in triple negative breast cancer (Kashiwagi et al., 2010; 20551954, Tang et al., 2011; 21519872). Presently, there are no targeted therapies to address loss of CDH1/E-cadherin.

- Interpretations are typically produced by paid curators with no provenance and no mechanism for feedback
- This effort would be enhanced by a public domain effort

Resources to help interpret clinical relevance



Resources providing clinical interpretations of mutations are the most lacking

- [ClinVar](#)
- [ClinGen](#)
- [CIViC](#) (cancer specific)
- Update this and reduce cancer focus
- Many ad hoc “databases” at academic centers and hospitals
- Commercial software solutions, pharmaceutical companies, etc.

CIViC was created to fill gaps in these resources

- www.civicdb.org
- Information on the clinical impact of many cancer variants is scattered throughout the published literature
 - This makes collecting that information both time and labor-intensive
 - Yet we are all repeating each others efforts...
- CIViC could act as a centralized forum for curation, interpretation, and debate
- Existing resources do not facilitate computational access
 - No APIs, not open source, not open access, etc.
- Goal: facilitate automated report generation on clinical variants

CIViC BETA

Site navigation: Go to Genes & Variants, GENE, BROWSE, SEARCH, ACTIVITY, ADD.

Edit content: GENE FLT3.

Gene-level interpretation: FLT3 is an important cytokine receptor involved in normal hematopoiesis. Mutations in this gene are common in acute myeloid leukemia (AML), and screening for mutations in this gene has been recommended by the World Health Organization in patients with AML, particularly in cases of cytogenetically normal AML (CN-AML). FLT3 mutations commonly co-occur with mutations such as NPM1 that are associated with CN-AML, and likely modulate prognostic impact. While FLT3-ITD mutations have been associated with poorer prognosis in AML, the prognostic impact of FLT3-TKD mutations are still up for debate.

Sources: Verdin et al., 2009. Blood. Strelakova et al., 2005. Int. J. Cancer.

Imported gene information: Name: fms related tyrosine kinase 3, Ensembl Symbol: FLT3, Ensembl ID: 23222, Aliases: CD135, FLK2, FLG2, STK1, Chromosome: 13 Start: 28577411 End: 28574729 Strand: -1 (ENST00000241493.7), Protein Domains: Immunoglobulin, Immunoglobulin-like domain, Protein kinase domain, Protein kinase, ATP binding site, Protein kinase-like domain... (3 more), Pathways: Pathway_PAT50954629, Sorafenib, Pharmacodynamics, Cytokine-cytokine receptor interaction - Homo sapiens (human), Hematopoietic cell lineage - Homo sapiens (human), Pathways in cancer - Homo sapiens (human)... (3 more).

View MyGene.info Details

Gene variant navigation: FLT3, DB035, DB035H, DB035H/Y, ITD, MUTATION, OVEREXPRESSION, T227M, TKD MUTATION, Add Variant Group.

Sequence ontology: Variant Type: Inframe Insertion.

Variant-level interpretation: Last Modified by [User], Last Reviewed by [User].

Variant coordinates: Reference Build: GRCh37, Ensemble Version: 75, Chromosome: 13, Start: 28568219, Stop: 28568311, Reference Bases: -, Variant Bases: -, Rep. Transcript: ENST00000241493.7, Edit Coordinates.

Data download/table legend: Get Data, Help.

Evidence records: Evidence for ITD (27 total items). EID 0E8G, 0E8I, DRUGS, EL, ET, EP, CS, VD, TR.

EID	0E8G	0E8I	DRUGS	EL	ET	EP	CS	VD	TR
190	Meta-analysis of studies...	Acute Myeloid Leukemia	N/A	A	A				2 *
69	In AML patients with FL...	Acute Myeloid Leukemia	N/A	B	A				5 *
1818	In the absence of a FLT3...	Acute Myeloid Leukemia	N/A	B	A				5 *
298	Sorafenib is effective in	Acute Myeloid Leukemia	Sorafenib	B	A				4 *

EVIDENCE EID190: Submitted by [User], Accepted by [User].

Evidence Summary: Evidence Level: A-Validated, Evidence Type: Prognostic, Evidence Direction: Supports, Clinical Significance: Poor Outcome, Variant Origin: Somatic Mutation.

Evidence Talk: Suggested revision notice.

Disease ontology: Disease: Acute Myeloid Leukemia.

Primary literature source: Drug: N/A, Citation: Poni et al., 2014. Ann. Hematol.

Trust Rating: ★ ★ ★ ★

User activity/attribution: Disclaimer: This resource is intended for purely research purposes. It should not be used for emergencies or medical or professional advice.

Evidence record details: Disclaimer: This resource is intended for purely research purposes. It should not be used for emergencies or medical or professional advice.

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Glossary of Terms, API Documentation, Data Releases, Presentation Graphics, Contact.

Extensive documentation: Glossary of Terms, API Documentation, Data Releases, Presentation Graphics, Contact.

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Features of CIViC

- Browse evidence records for variant-drug-disease relationships as well as diagnostic and prognostic biomarkers
- Curation/ crowdsourcing interface
- Expert review
- Structured data model
- Use of existing ontologies
- JSON API to automate report generation