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- OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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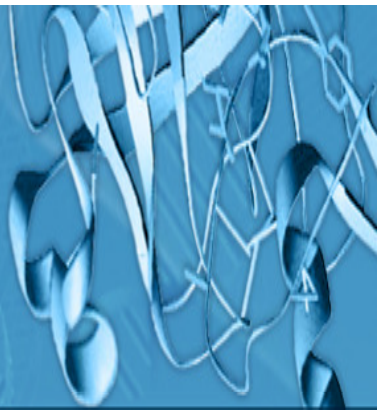
Translating multidimensional cancer omics data into biological insights



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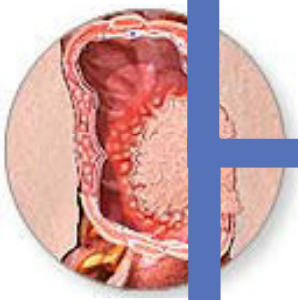
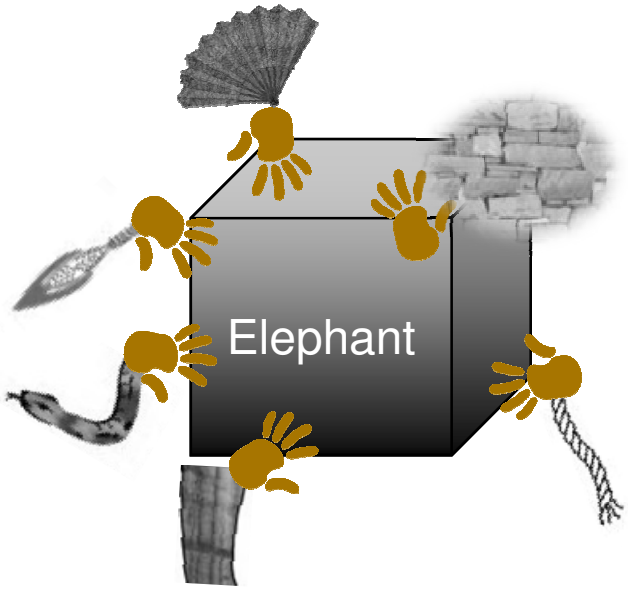
Omics opportunities and challenges

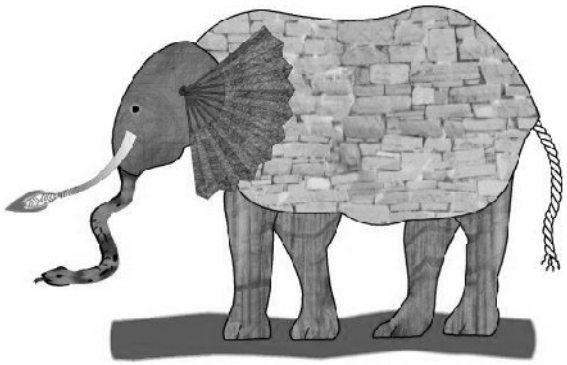


DNA
CNV
mutation
methylation

mRNA
expression
splicing

Protein
expression
modification





- Risk
- Diagnosis
- Prognosis
- Therapeutics

The Cancer Genome Atlas (TCGA)
Colon and Rectal Cancer (CRC) Project

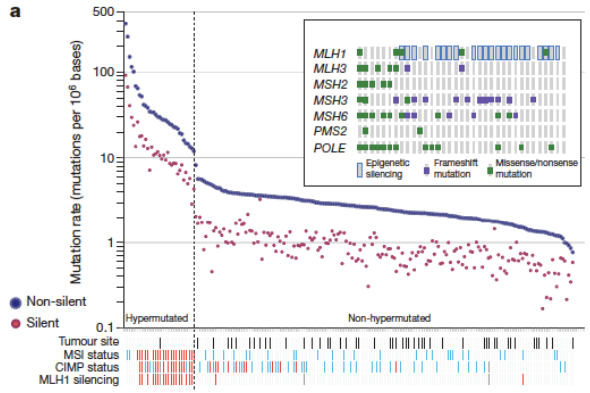
ARTICLE

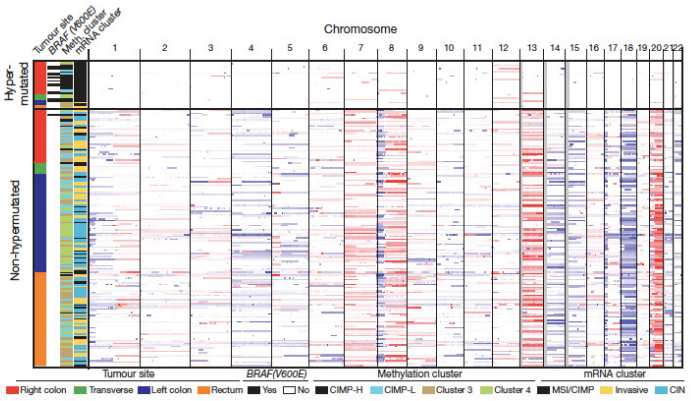
doi:10.1038/nature11252

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

Nature (2012) 487: 330-337





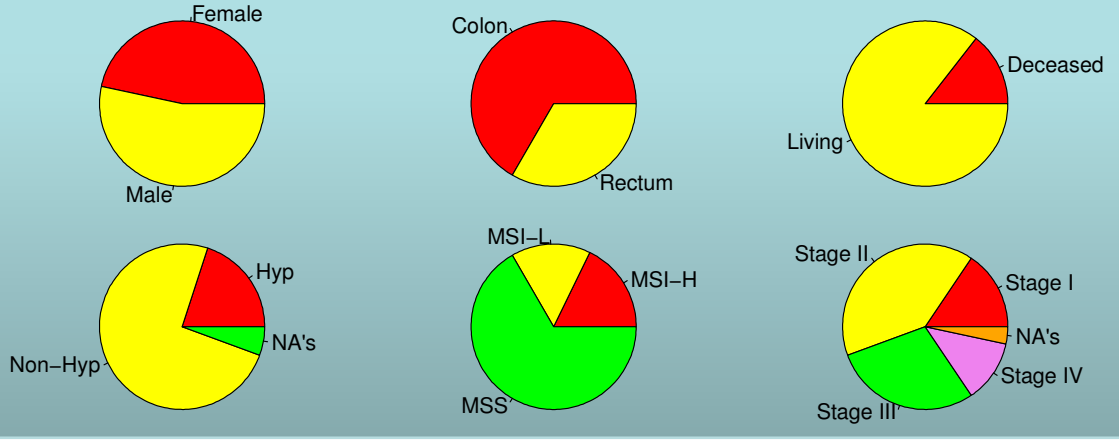
- Hypermutator genotype
- Somatic mutations
- Copy number alterations
- Translocations
- Transcriptomic subtypes

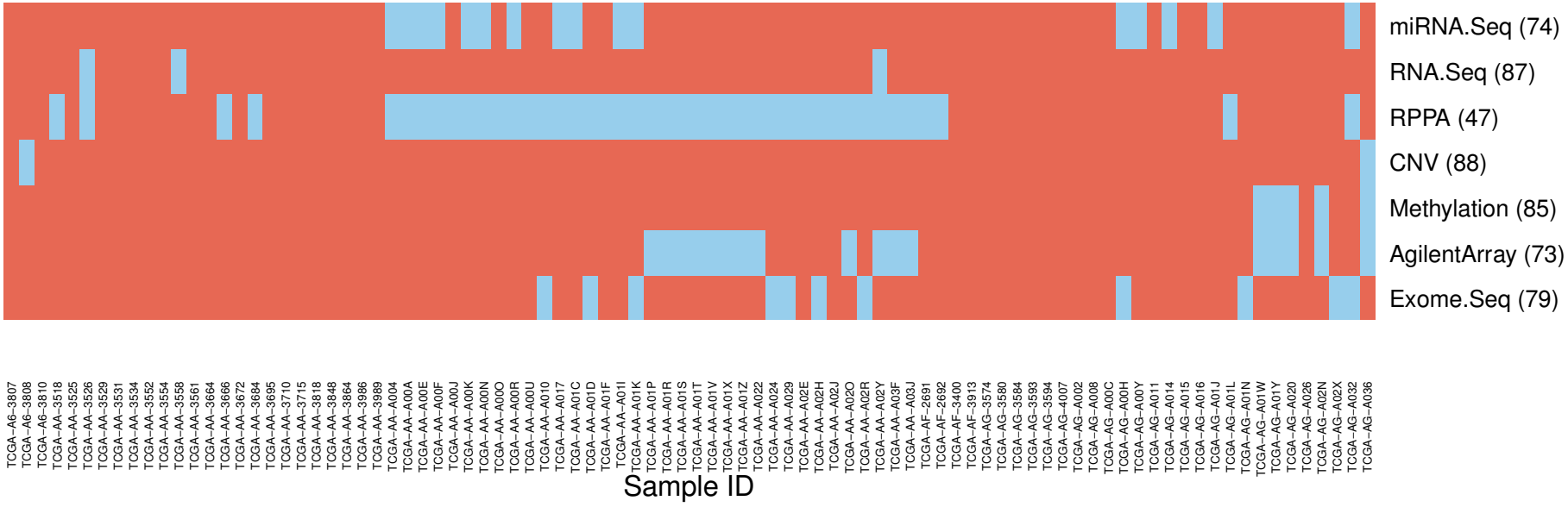
How genomic alterations drive cancers?

Clinical Proteomic Tumor Analysis Consortium (CPTAC)

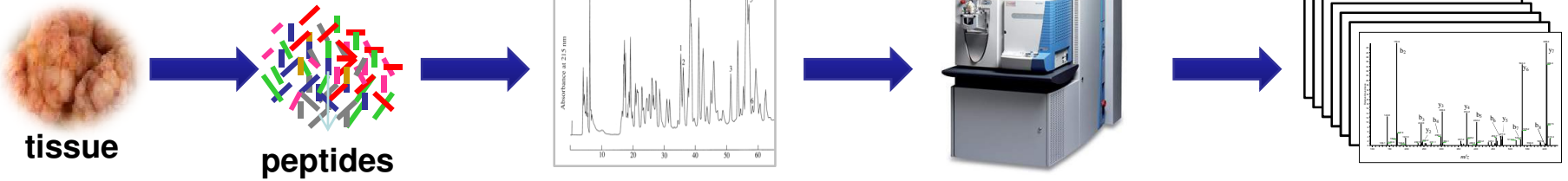
Global proteomics analysis: Samples

Clinical characteristics of the 90 colorectal cancer (CRC) samples





Global proteomics analysis: Vanderbilt shotgun proteomics platform



Digestion
(TFE, trypsin)

bRPLC
15 concatenated fractions

LC-MS/MS
Thermo Orbitrap-Velos

MS/MS spectra

Protein	MMR+	MMR-	LogRatio	Quasi_FDR	Total	T1A	T1B	T1C	T1D	T1G	T1H	T1I	T1J	T10A	T10B	T10C	T10D	T10E	T2B	T2D	T2F	T2G	T2I
CEACAM7	88	73	0.269271	1.162347	190	0	0	0	0	0	0	0	0	0	2	0	1	0	7	1	0	0	9
FAM203A	92	76	0.275305	1.441032	198	1	5	1	4	2	1	4	5	7	1	0	0	1	4	1	4	1	4
DSCAML1	29	15	0.946471	0.999179	46	0	0	0	1	0	1	1	0	1	1	0	0	0	1	0	0	0	1
GSTT1	157	128	0.294413	1.419495	325	1	0	1	3	5	8	2	1	8	3	16	5	1	1	1	12	14	9
SLMAP	199	162	0.296609	1.173767	421	1	1	0	5	24	3	4	3	0	3	9	4	1	4	3	1	66	3
MXRA5	215	174	0.305091	1.243149	379	0	0	0	12	3	1	8	0	12	1	13	2	1	3	32	6	0	0
ISY1	29	15	0.946471	0.9992	48	1	0	0	0	0	1	1	4	1	0	0	1	1	0	0	1	0	1
CARS2	171	138	0.309126	1.435068	369	9	7	8	9	1	11	5	6	4	2	5	2	0	7	0	10	0	8
PCCA	506	408	0.3105	1.508151	1104	9	5	23	13	7	12	20	10	12	20	6	4	3	31	4	22	6	10
ACOT8	178	143	0.315664	1.436292	374	6	7	3	6	1	2	7	20	3	1	3	2	6	8	3	5	0	2
NDUFAF2	146	117	0.319215	1.455778	321	3	7	8	6	1	11	2	14	7	1	2	2	5	8	0	5	0	4
KAT8	29	15	0.946471	0.999221	47	0	1	0	1	1	2	0	1	1	0	0	0	0	1	0	1	1	2
CEACAM6	322	257	0.325179	1.293481	637	0	7	6	7	3	0	0	5	5	3	3	3	9	28	32	19	0	12
TSPYL1	2	1	0.932886	0.999227	3	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
PPP1R1B	103	82	0.32859	1.230522	241	0	2	2	0	0	1	0	6	27	2	2	3	2	2	0	0	0	1
ERAP2	259	206	0.330165	1.235779	508	12	0	2	4	3	0	5	0	16	1	3	0	1	1	0	0	0	6
MRPL22	117	93	0.330888	1.434399	257	1	2	5	3	2	12	8	7	1	2	2	0	0	5	0	5	0	1
NUBP1	126	100	0.333126	1.480498	259	3	1	1	2	3	5	1	6	2	1	1	2	0	4	3	2	0	3
MRPS30	86	68	0.338358	1.358032	186	1	2	3	2	0	7	3	2	9	2	2	0	1	4	0	3	0	0
PGM5	661	519	0.348856	1.227494	1315	0	0	3	1	48	3	0	1	9	32	63	4	0	3	0	4	149	3
LPGAT1	29	15	0.946471	0.999269	48	1	0	0	0	0	3	2	1	1	0	1	1	2	0	0	0	0	0
BDH2	79	62	0.349084	1.353335	156	0	0	0	5	1	1	0	4	0	4	3	0	0	3	0	6	0	1
MLKL	31	16	0.949854	0.99928	50	0	2	1	0	1	2	1	2	0	0	0	0	0	1	0	0	0	0
EDC3	54	28	0.945058	0.999286	81	2	1	0	2	0	0	5	3	2	1	0	0	1	1	0	1	1	1
PIGK	71	37	0.93843	0.999289	112	2	2	2	2	0	1	2	0	2	1	2	1	1	1	1	2	0	0
LPPR3	2	1	0.932886	0.999289	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SPAG6	2	1	0.932886	0.999293	3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
ALG1	90	47	0.9358	0.9993	143	0	4	2	2	1	3	2	3	1	3	3	2	3	3	1	2	1	2
TTR	291	228	0.351848	1.345473	527	1	0	1	0	2	4	0	1	4	3	4	8	9	4	39	7	14	6
SYNPO2	776	608	0.351934	1.160705	1575	0	0	0	4	77	10	4	4	2	20	72	7	0	2	0	2	265	2
HNF4A	96	75	0.355724	1.409905	201	3	1	3	4	5	2	6	6	2	0	1	1	2	2	0	3	0	3
RBM26	84	44	0.931327	0.999308	135	2	2	3	1	0	2	3	2	1	1	0	2	1	1	0	3	0	0
PRKG1	82	64	0.357058	1.32783	165	2	1	0	6	6	0	2	0	1	0	3	4	2	1	2	1	11	0
SPEN	44	23	0.932886	0.999316	68	0	1	0	0	1	2	2	1	0	2	1	0	0	1	2	3	0	1
AGFG2	17	9	0.910058	0.999323	26	1	1	0	0	0	1	0	1	0	0	0	0	0	1	0	1	0	0

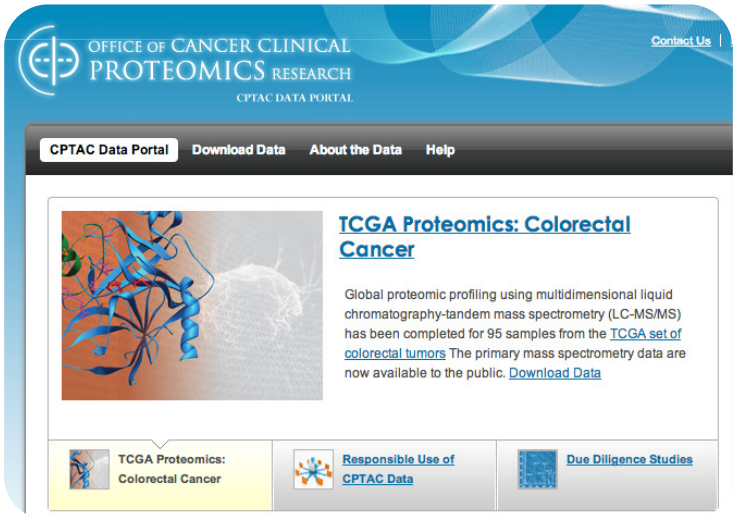
Preprocessing
- MSConvert

Peptide identification
- Myrimatch
- Pepitome
- MS-GF+

Protein assembly
- IDPicker

Global proteomics analysis: Summary of the proteomics data

- 90 tumors
- 6,299,756 identifiable spectra
- 124,823 distinct peptides (1% FDR)
- 7,526 proteins (2.6% FDR)
- 3,899 quantifiable proteins (0.43% FDR)



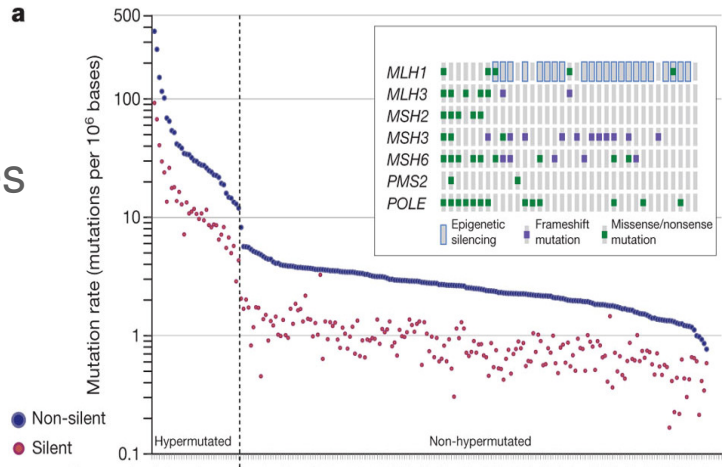
https://cptac-data-portal.georgetown.edu

What is the added value of proteome profiling in human cancer studies?

- Cancer biomarker discovery
- Oncogenic driver prioritization
- Molecular subtype classification

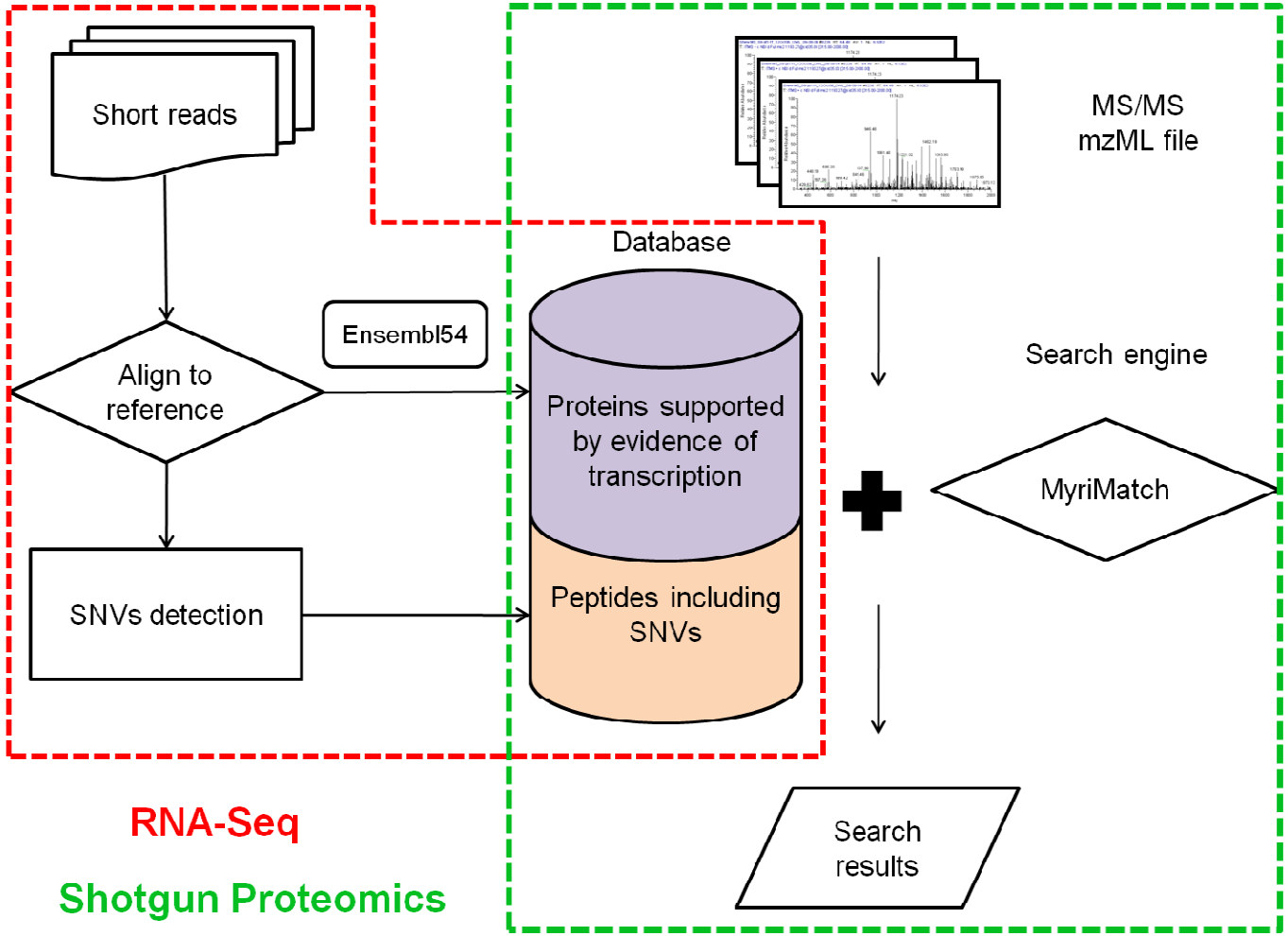
Mutant proteins as cancer biomarkers

- Proteins resulting from somatic mutations are ideal cancer biomarkers
  - Specificity
    - Unlike CEA and PSA
  - Possible drivers
    - Not only association
  - Established targeted proteomics technologies
    - Selected Reaction Monitoring (SRM)
    - Multiple Reaction Monitoring (MRM)
- Many somatic mutations have been identified in the TCGA studies
- **Can we prioritize somatic mutations for targeted analysis?**



TCGA. Nature, 2012

Personalized protein database from RNA-Seq data



- Increased sensitivity
- Reduced ambiguity
- Variant peptides

customProDB is available in Bioconductor

Wang et al., J Proteome Res, 2012
Wang & Zhang, Bioinformatics, 2013

Personalized database search results

- 1,065 variant peptides
- 796 unique Single Amino Acid Variants (SAAVs)
  - 64 in TCGA reported somatic variations
  - 101 in the COSMIC database
  - 526 in the dbSNP database
- 647 variant proteins
  - Known cancer genes: KRAS, CTNNB1, SF3B1, ALDH2, FH, etc.
  - Targets of FDA approved drugs: ALDH2, HSD17B4, PARP1, P4HB, TST, GAK, SLC25A24, SUPT16H, etc.

What is the added value of proteome profiling in human cancer studies?

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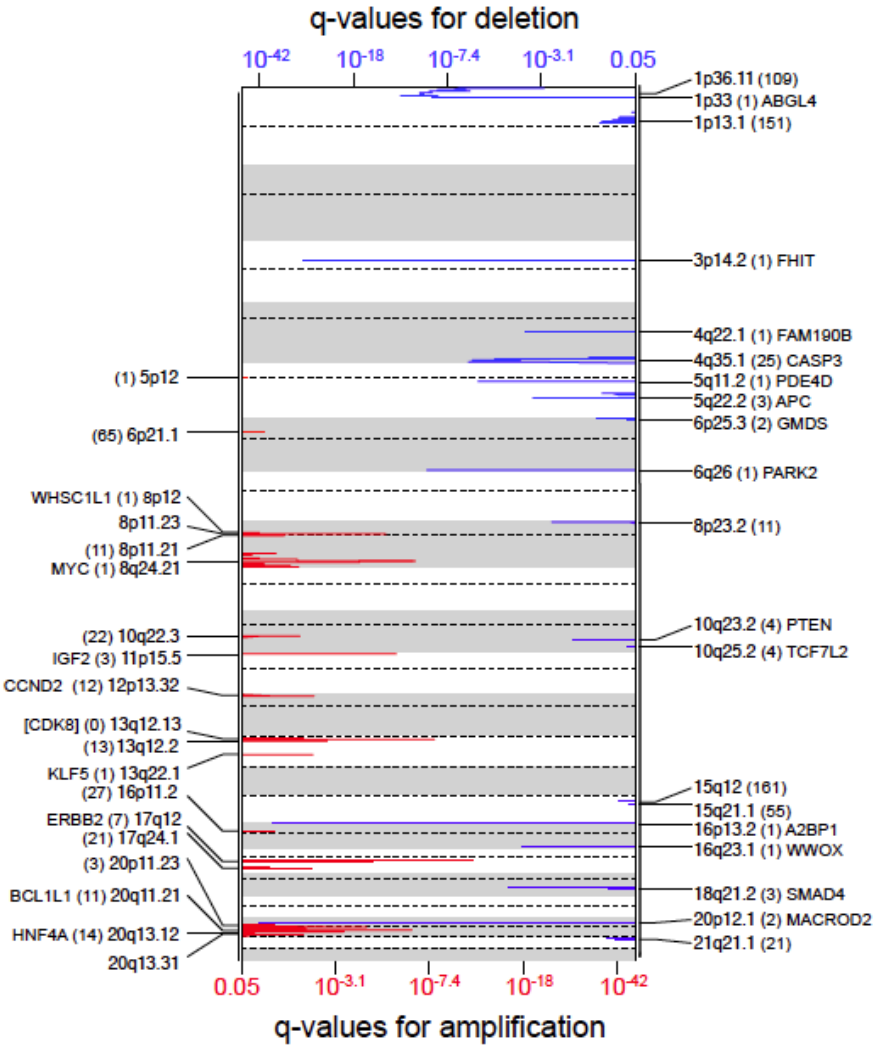
- Oncogenic driver prioritization
- Molecular subtype classification

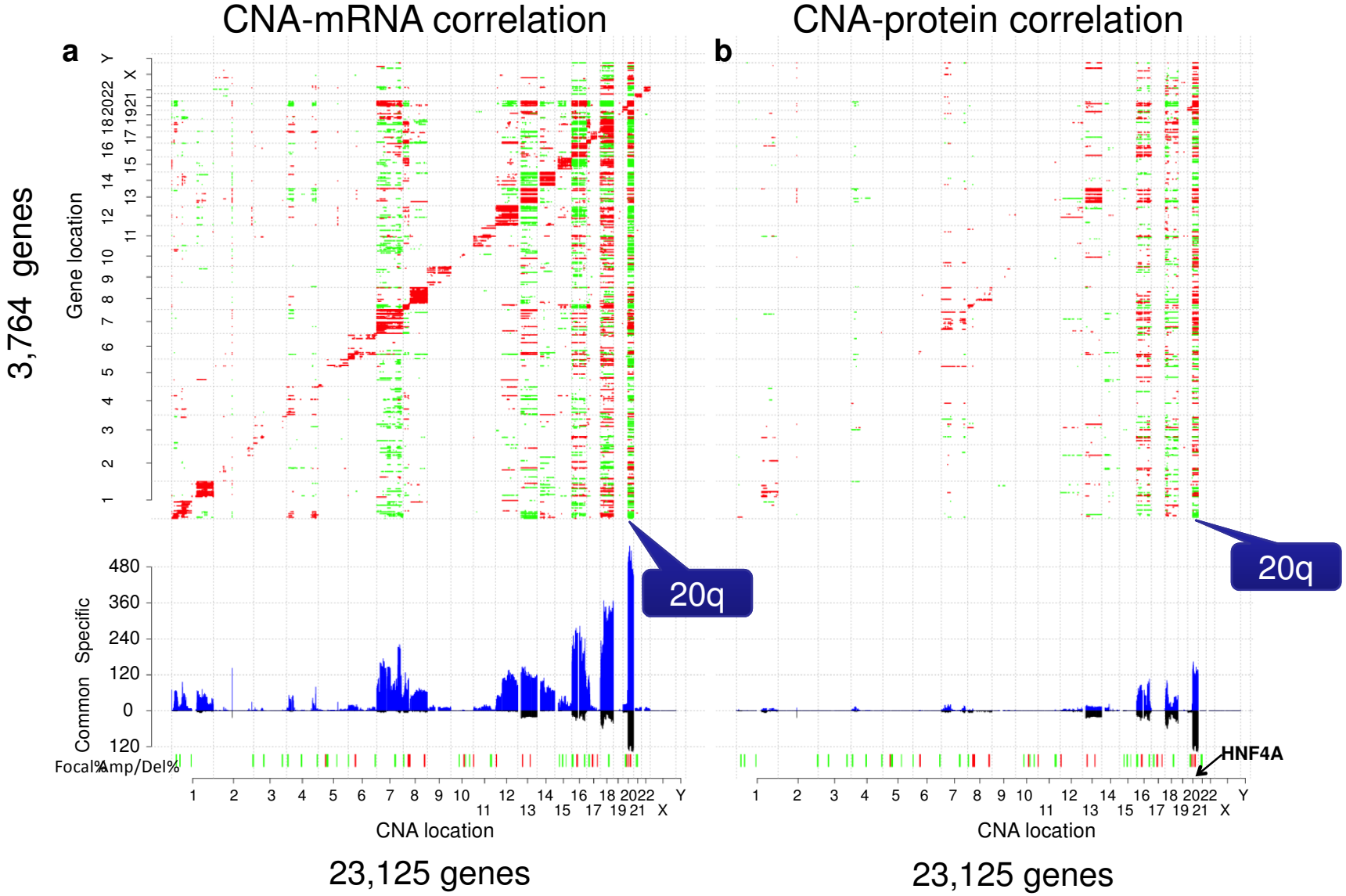
Candidate drivers in regions of copy number alteration (CNA)



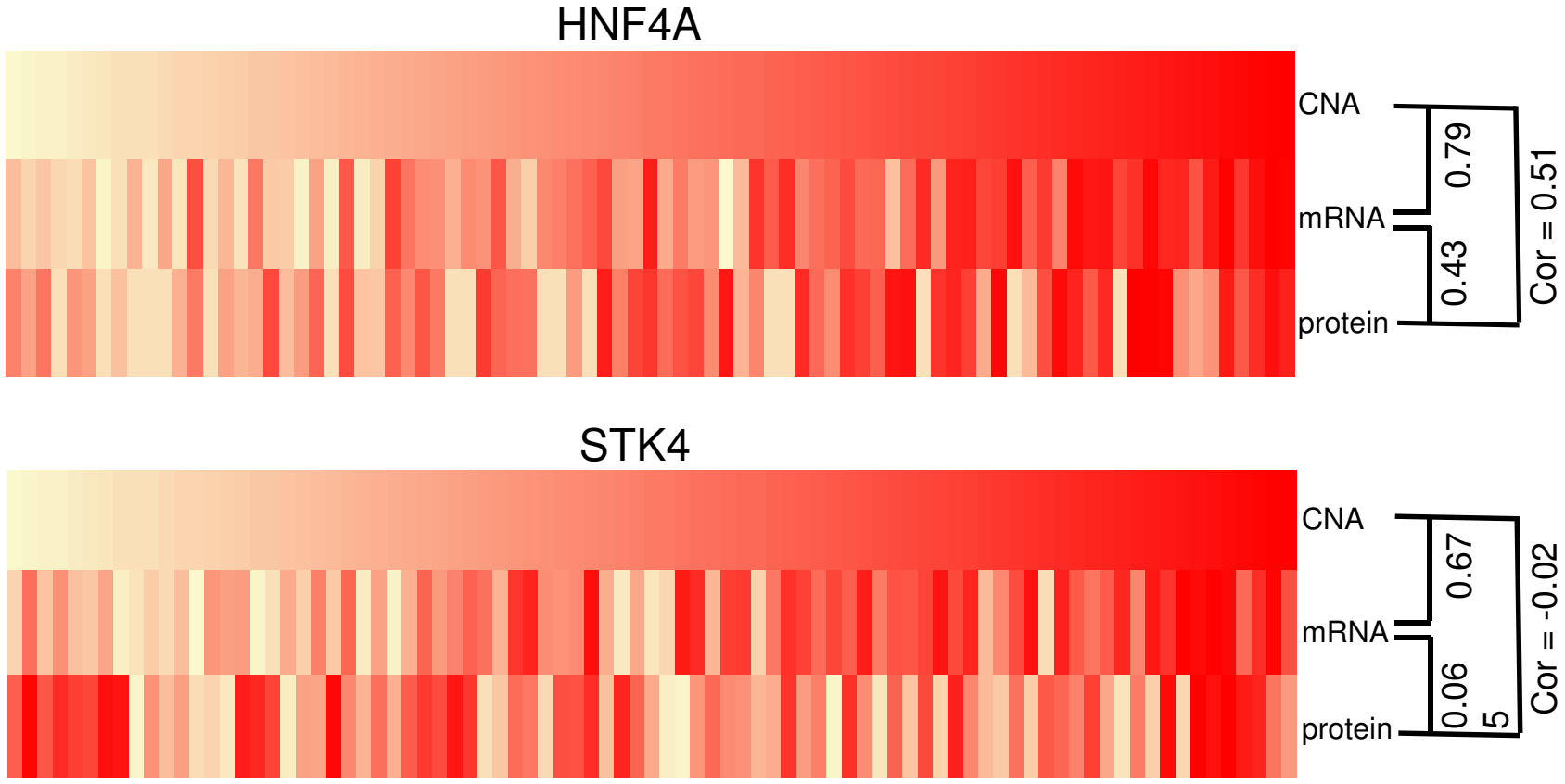
TCGA. Nature, 2012

- The TCGA study identified 17 focal amplification regions and 28 focal deletion regions
- CNA-mRNA correlation has been widely used for the prioritization of candidate drivers
  - *Wang et al. Clin Cancer Res, 2013*
- **What can proteomics tell us about these regions and candidate drivers?**

Proteomics data enables prioritization of CNA regions and candidate drivers

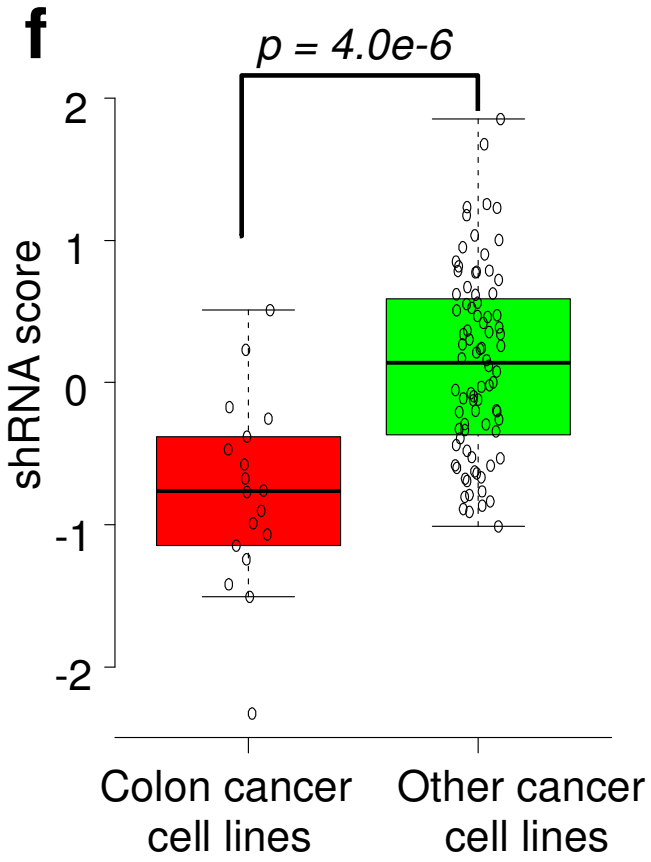


Proteomics data help narrow down candidate oncogenic drivers



Two genes in the focal amplification region 20q13.12

Higher HNF4A dependency in CRC cell lines



Data from the Achilles project
http://www.broadinstitute.org/achilles

What is the added value of proteome profiling in human cancer studies?

- Cancer biomarker discovery
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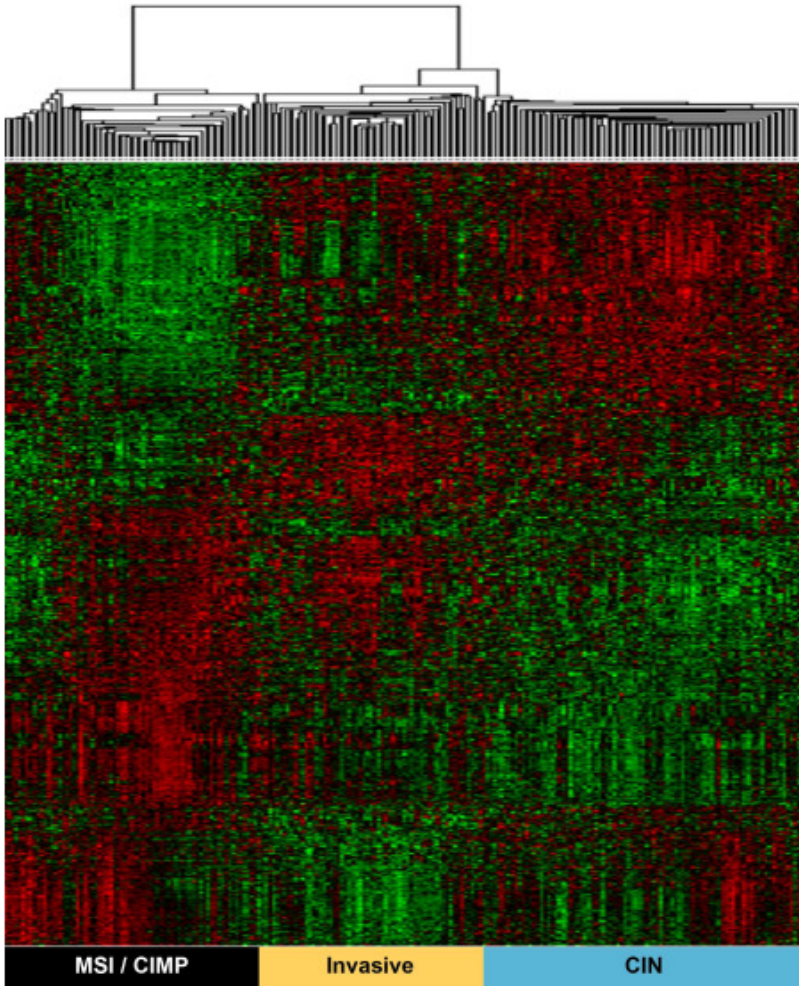
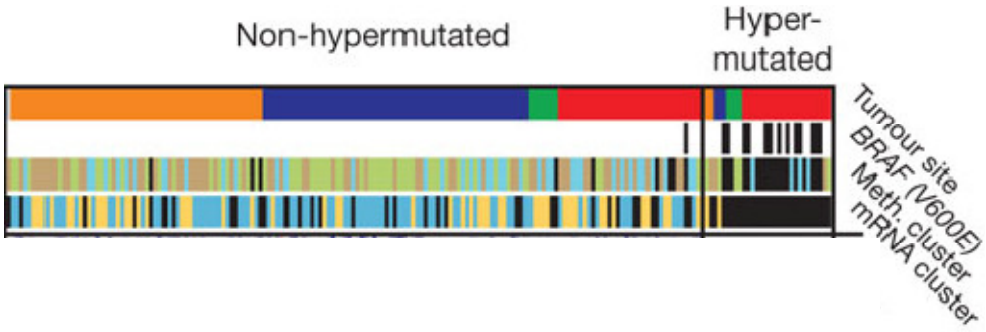
- Molecular subtype classification

TCGA transcriptomic subtypes

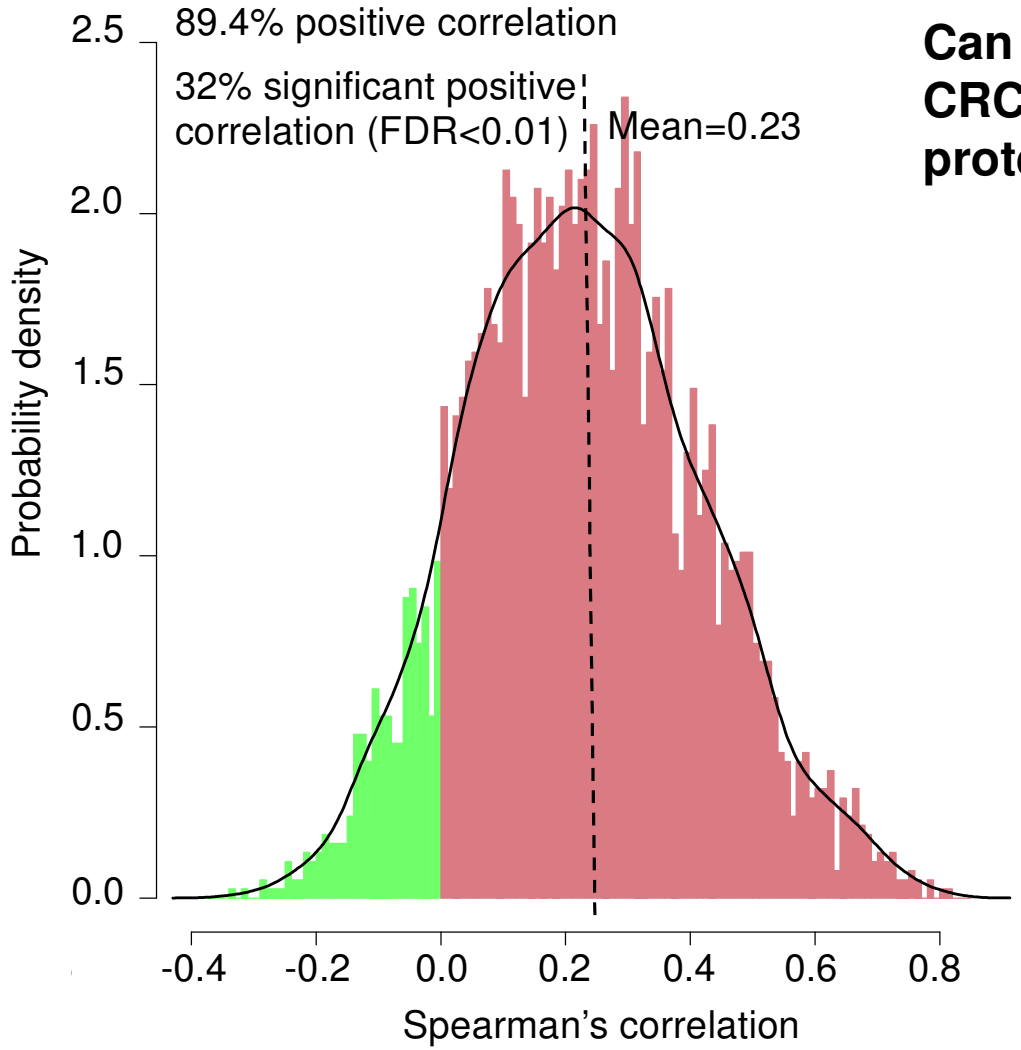




- The TCGA study identified three transcriptomic subtypes: **MSI/CIMP** (Microsatellite instability/ CpG island methylator phenotype), **Invasive**, and **CIN** (Chromosome Instability)
- The MSI/CIMP subtype is enriched with hypermutated tumors

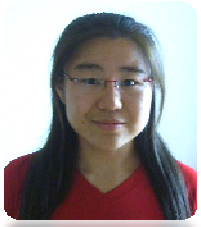
TCGA. Nature, 2012

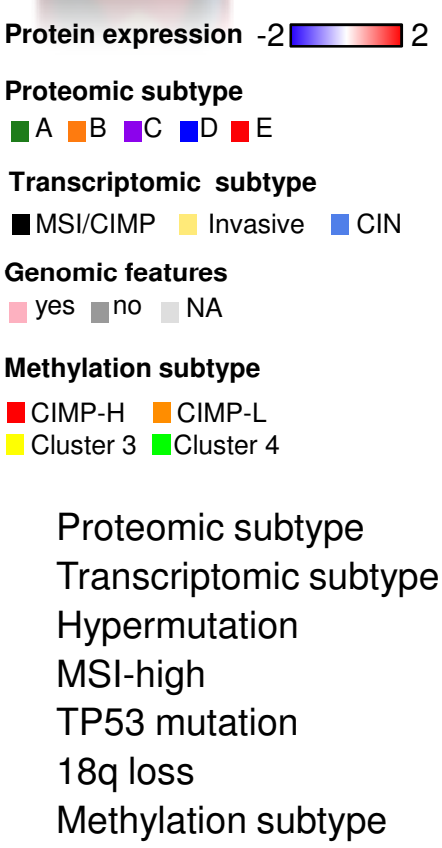
mRNA level does not reliably predict protein level

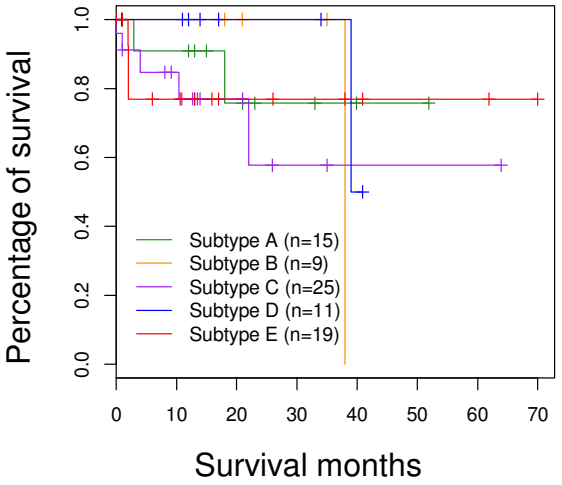


Can we rediscover or redefine CRC subtypes using proteomics data?

Five proteomic subtypes

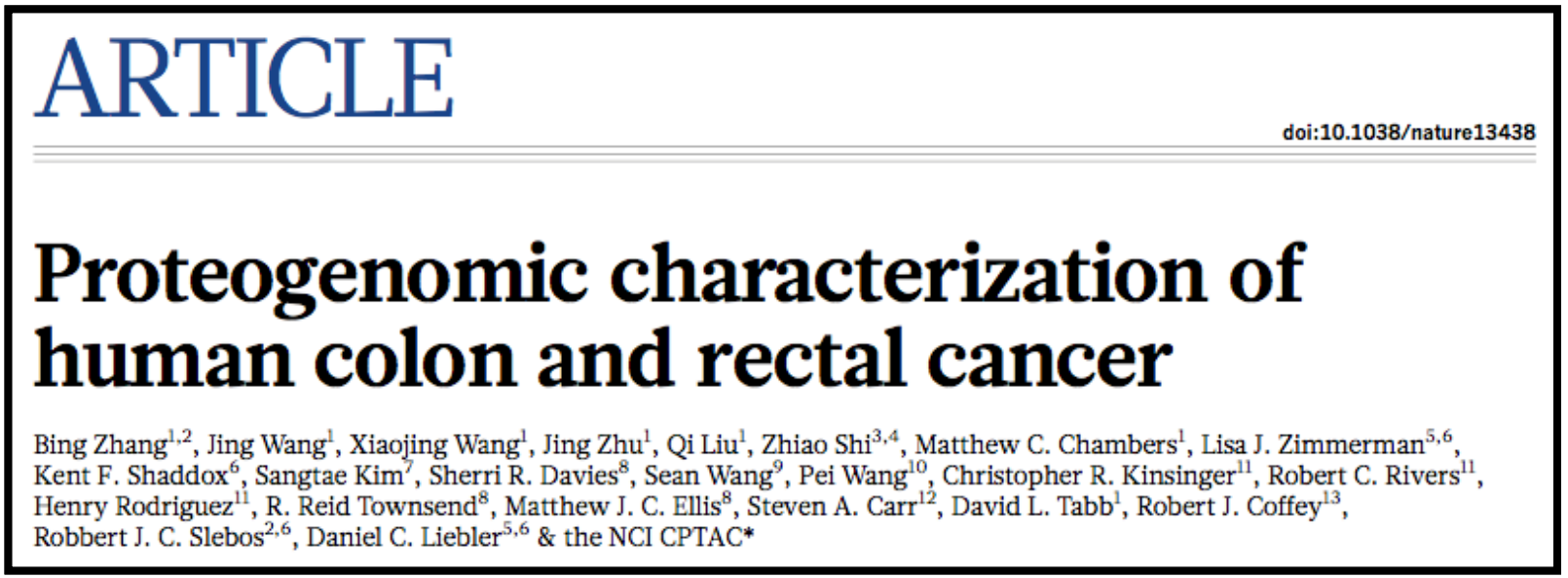






Summary

- Integrated proteogenomic analysis may enable new advances in cancer biology and management.
  - Identifying mutant peptides as candidate cancer biomarkers
  - Prioritizing oncogenic drivers in focal amplification regions.
  - Revealing molecular subtypes that cannot be distinguished using mRNA expression data.



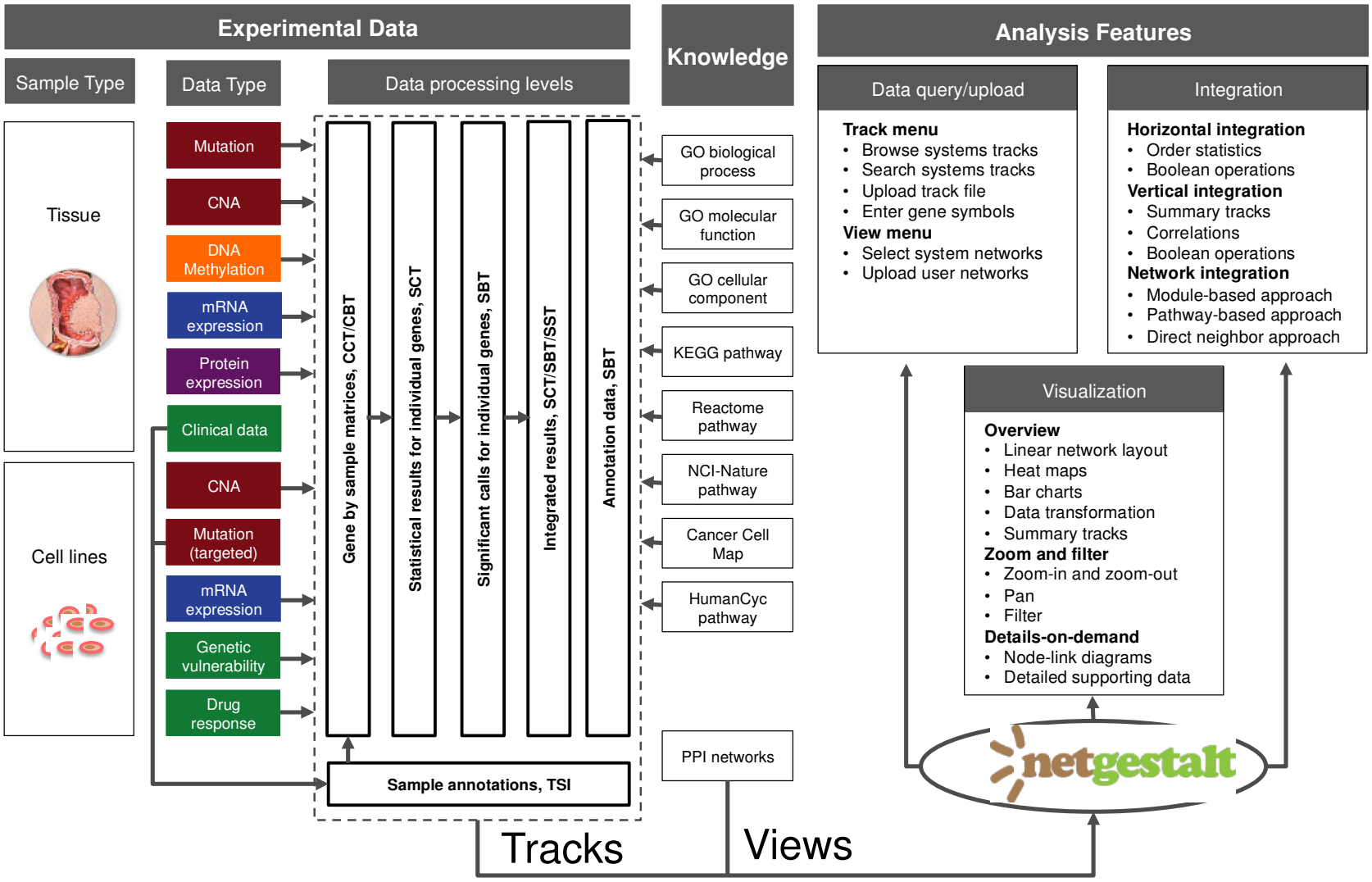
ARTICLE

doi:10.1038/nature13438

Proteogenomic characterization of human colon and rectal cancer

Bing Zhang[1,2], Jing Wang[1], Xiaojing Wang[1], Jing Zhu[1], Qi Liu[1], Zhiao Shi[3,4], Matthew C. Chambers[1], Lisa J. Zimmerman[5,6], Kent F. Shaddox[6], Sangtae Kim[7], Sherri R. Davies[8], Sean Wang[9], Pei Wang[10], Christopher R. Kinsinger[11], Robert C. Rivers[11], Henry Rodriguez[11], R. Reid Townsend[8], Matthew J. C. Ellis[8], Steven A. Carr[12], David L. Tabb[1], Robert J. Coffey[13], Robbert J. C. Slebos[2,6], Daniel C. Liebler[5,6] & the NCI CPTAC*

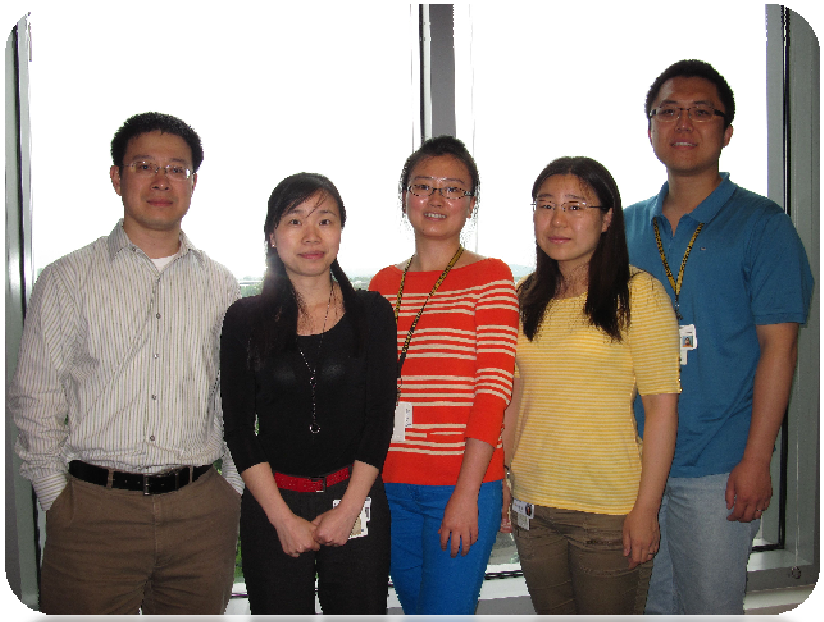
Making data accessible and reusable
NetGestalt CRC portal (http://crc.netgestalt.org)



Shi et al. Nature Methods, 2013

Acknowledgement

- Jing Wang
- Qi Liu
- Xiaojing Wang
- Jing Zhu



- Dan Liebler
- Rob Slebos
- Dave Tabb
- Zhiao Shi
- CPTAC Network
- TCGA Network

Funding:
SAIC RFP S13-029
NCI U24 CA159988
NIGMS R01 GM088822
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