Individualized multi-omic pathway deviation scores using multiple factor analysis

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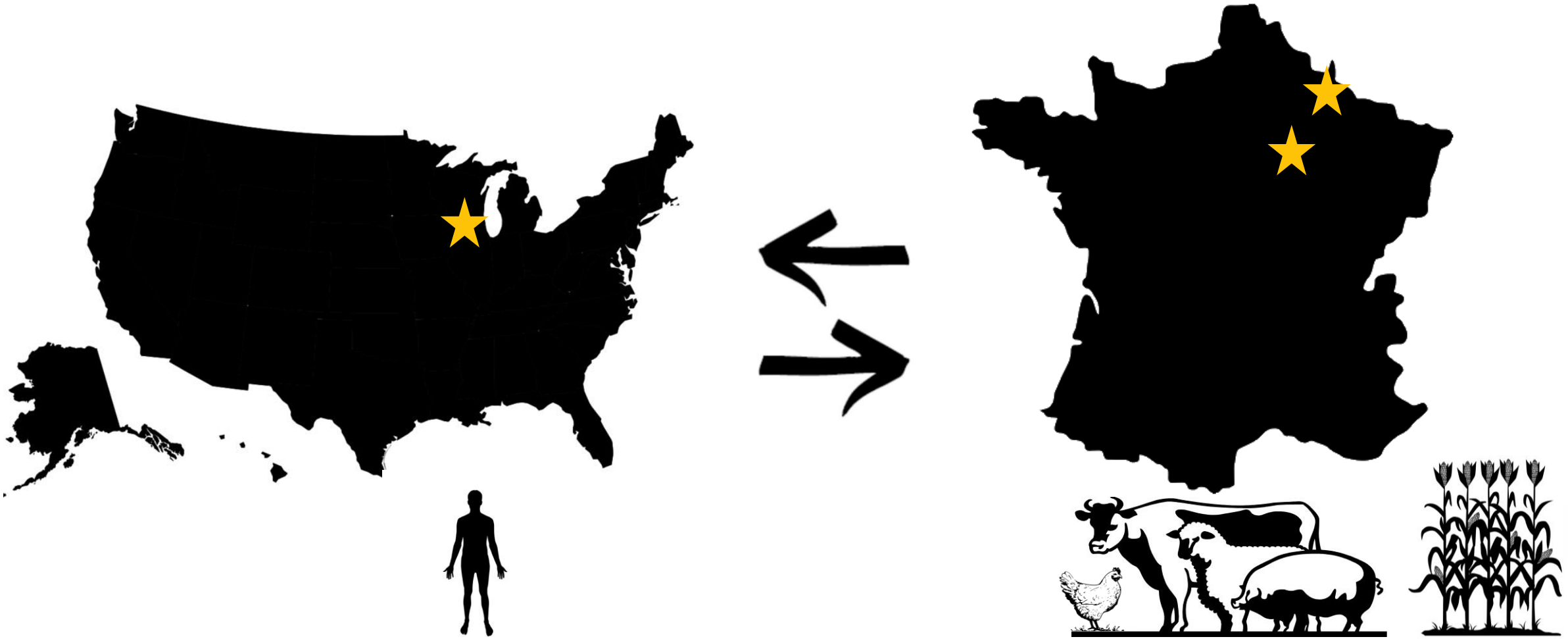
DECEMBER 9, 2019

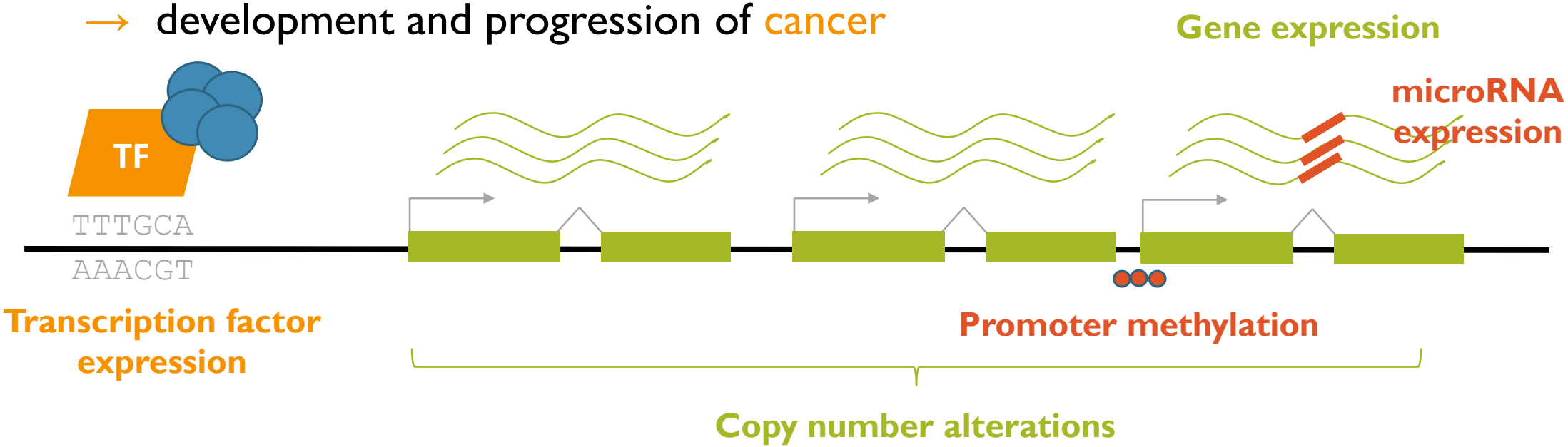


Transcriptional regulation (in cancer genomes)

Dysregulated genes regulating cell growth/differentiation

→ uncontrolled cell growth

→ development and progression of cancer



...GCAGCGTTCGA...

...GCAACGTTAGA...

→ **Somatic mutations** within tumors, **Germline genetic variation**

… + Chromatin accessibility + RNA processing + RNA stability + Protein activity + …

The Cancer Genome Atlas (TCGA)

- Comprehensive, **multi-dimensional maps** of key genomic changes in **33 cancer types** from **11k+ individuals**

- Publically available data (multi-tiered data depending on patient identifiability)

- **Widely** used by the research community (1000+ publications by TCGA network + independent researchers)

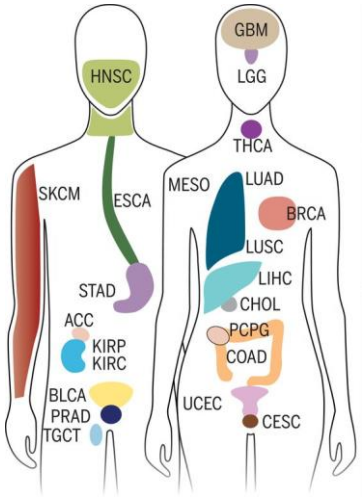
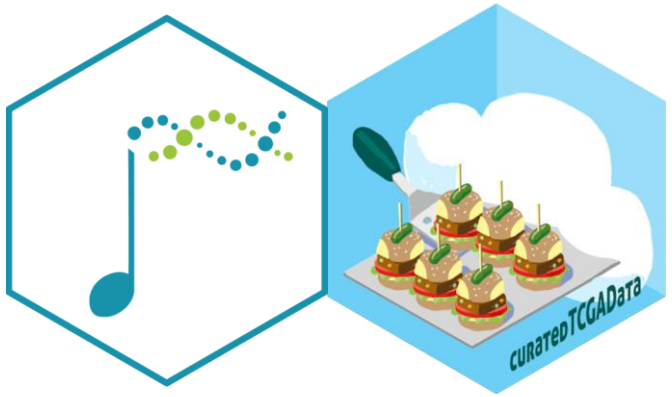


Image: Corces et al. (2018)



Multi-omic data → Multivariate, multi-table methods

- Account for **interdependencies** within and across data types

- (Partially) **matched** omics data across samples or biological entities (e.g., genes)

- In some contexts, limited/incomplete *a priori* knowledge of relevant phenotype groups for comparisons = **unsupervised analysis**

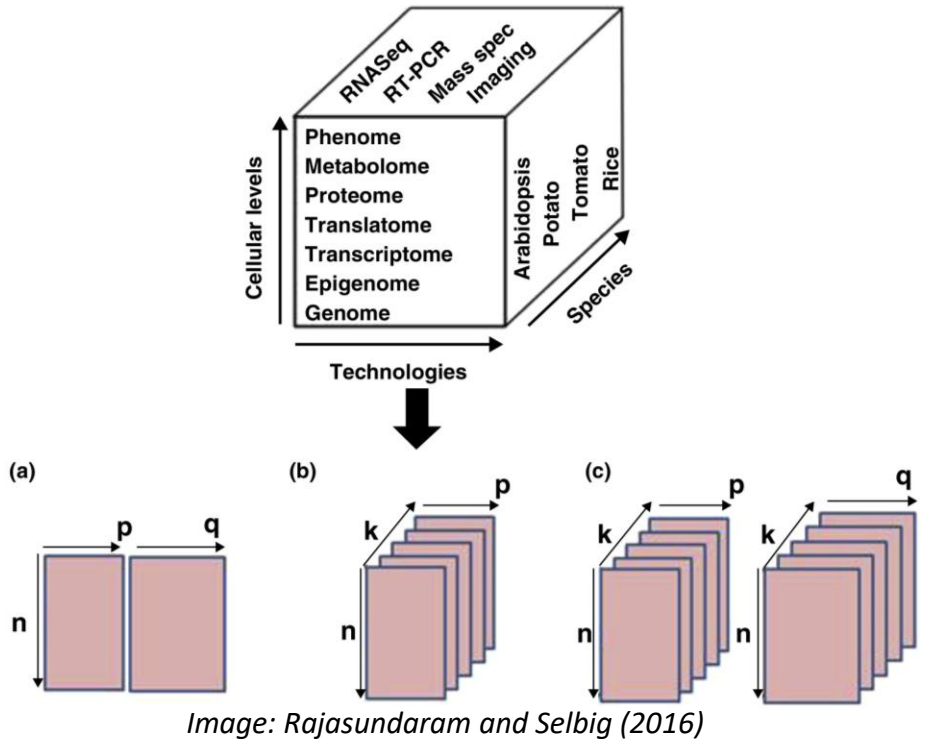


Image: Rajasundaram and Selbig (2016)

~~How do we integrate multi-omic data?~~

What question are we specifically addressing? How can we use multi-omic data to answer that question?

Our focus is specifically on pathway-level inference

reactome

BIOCARTA

For a given pathway of interest, can we **identify** and **quantify** highly **aberrant individuals** in a sample based on **multi-omic data**?

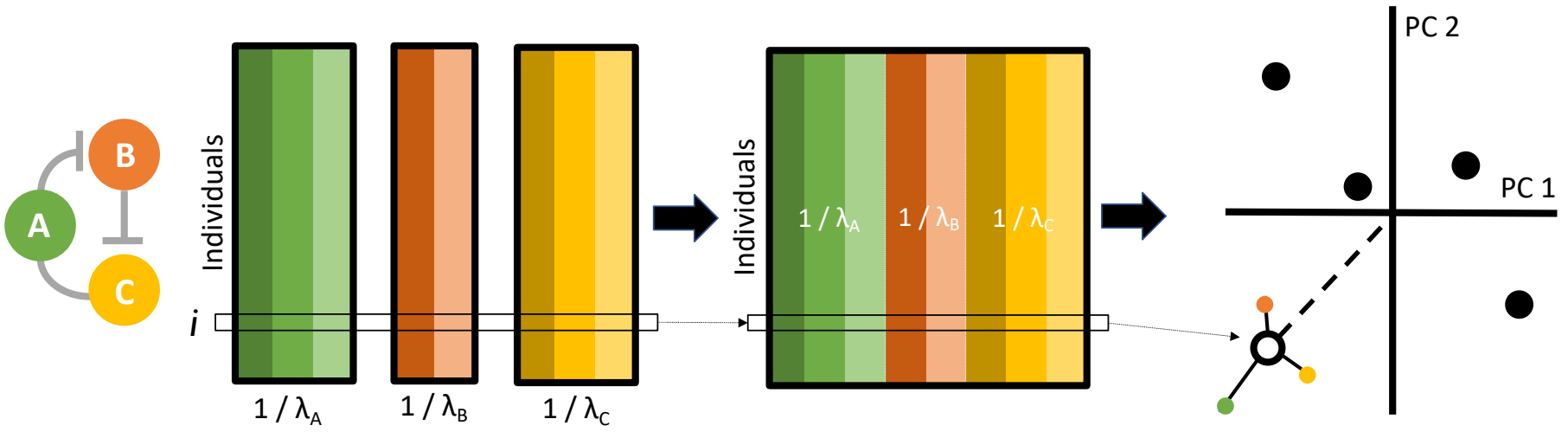
Does patient prognosis correlate with large pathway deviation scores?

Which individuals have the most aberrant profiles for pathways of interest?

Which genes / omic drive these aberrant scores?

padma: Pathway deviation scores using Multiple Factor Analysis

Define an *individualized* pathway-level deregulation score based on multi-omic data using **MFA**



Individualized pathway and per-gene deviation scores

In the multi-dimensional MFA consensus space, the origin represents the "average" pathway profile across genes, omics, and individuals.

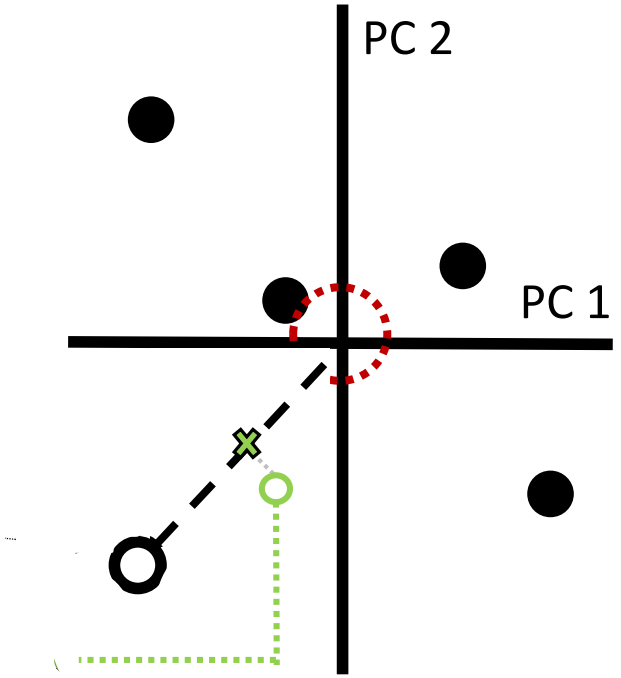
Pathway deviation score = Euclidean distance of MFA factors to the origin for each individual

$$d_i^2 = \sum_{l=1}^{L} f_{i,l}^2$$

Partial MFA factor scores can be computed for each gene

Decompose each pathway deviation score into ***per-gene deviation scores****

$$d_{i,g} = \frac{\sum_{l=1}^{L} f_{i,l}(f_{i,l,g} - f_{i,l})}{\sum_{l=1}^{L} f_{i,l}^2}$$



Richness of additional MFA outputs:

→ Decomposition of the total variance by MFA component

→ % contribution to the inertia of each axis by omic, gene, or individual

FACTOMINER

*We normalize the per-gene deviation scores by each individual's pathway deviation score.

Applying *padma* to TCGA data

Breast invasive carcinoma (**BRCA**; *n* = 504) and lung adenocarcinoma (**LUAD**; *n* = 144)

- Batch correction performed using removeBatchEffects in *limma*
- RNA-seq + promoter methylation + copy number alterations + miRNA-seq
- miRNA → gene mapping provided by miRTarBase (exact matches, Functional MTI predictions)

- **1136 MSigDB curated canonical pathways** (Biocarta, PID, Reactome, Sigma Aldrich, Signaling Gateway, Signal Transduction Knowledge Environment, Matrisome Project)

Patient prognosis measured using progression-free interval survival times (LUAD) and histological grade (BRCA)

For which pathways do large deviation scores correlate with poor prognosis?
Progression-free interval (LUAD)

- **14 pathways** significantly associated with survival (Cox PH*, BH padj < 5%)
- **Higher scores = worse outcome**
- Not linked to tumor mutational burden

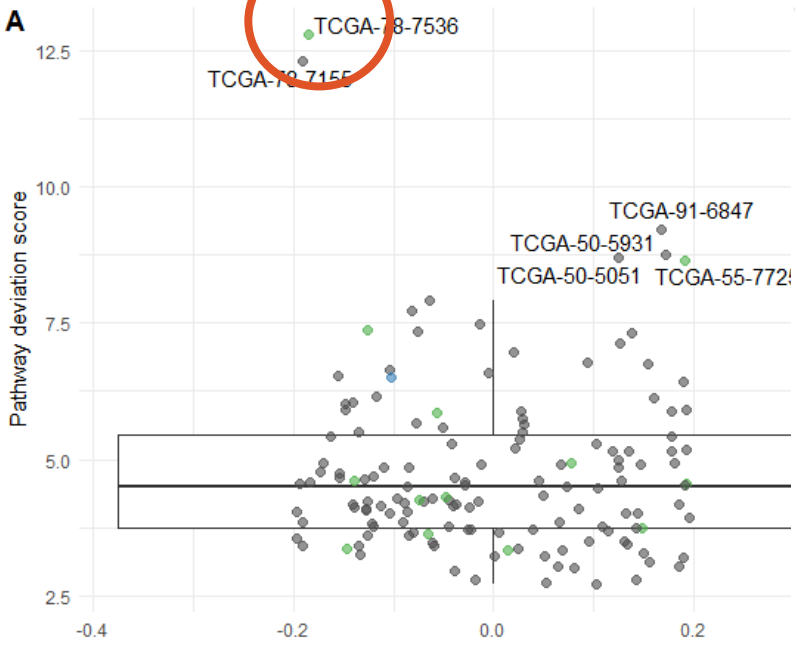
Pathway name	Database	Adj. p-value	Hazard ratio	# of genes
D4-GDI (GDP dissociation inhibitor) signaling pathway	Biocarta	0.0111	1.2692	13
NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10	Reactome	0.0111	1.2839	12
Class I PI3K signaling events mediated by Akt	PID	0.0251	1.1700	35
ATM signaling pathway	Biocarta	0.0265	1.1644	20
CARM1 and regulation of the estrogen receptor	Biocarta	0.0265	1.1426	35
Homologous recombination repair of replication-independent double-strand breaks	Reactome	0.0265	1.2432	16
Role of BRCA1, BRCA2, and ATR in cancer susceptibility	Biocarta	0.0467	1.1823	21
…	…	…	…	…

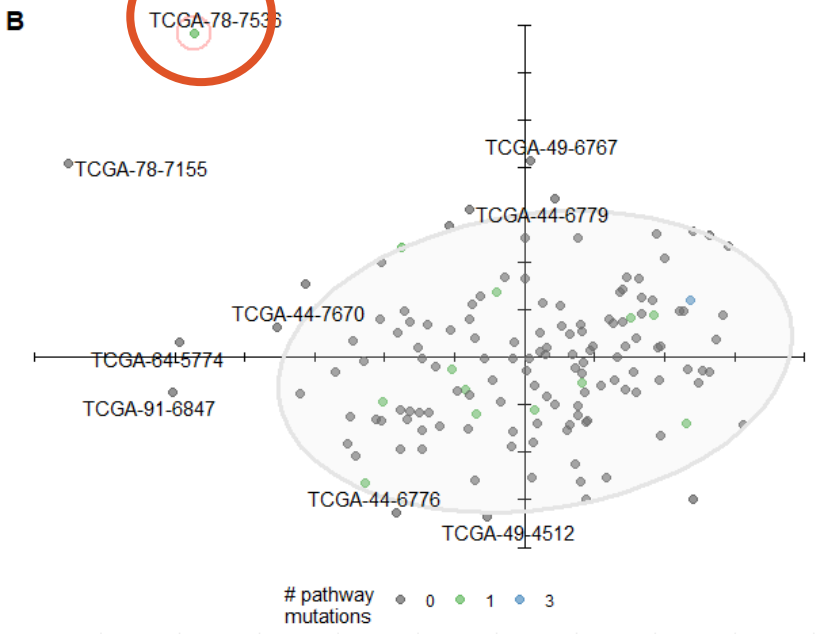
Focus on the D4-GDP dissociation inhibitor signaling pathway…

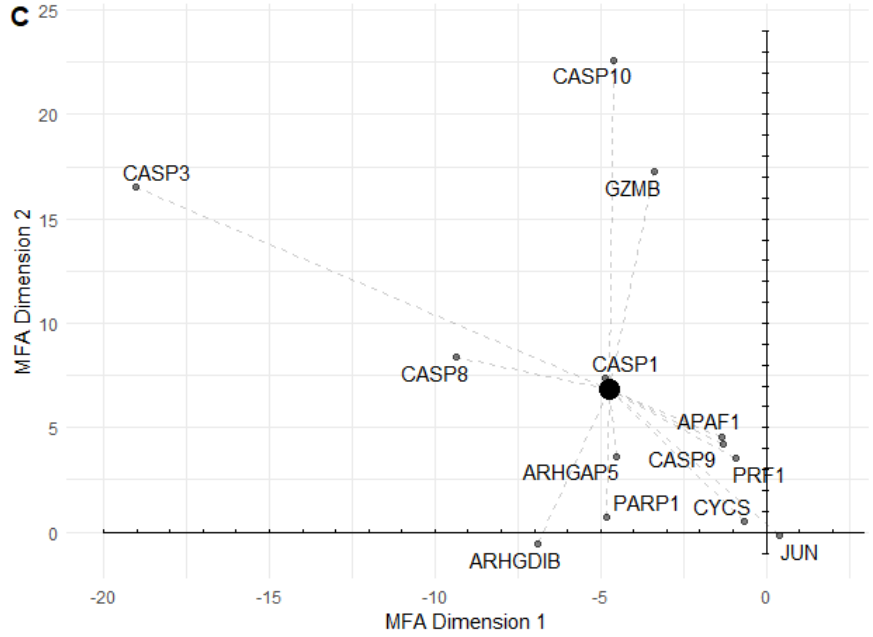
* Test performed on 5% most skewed pathways

Which individuals have the most highly aberrant multi-omic profiles?

D4-GDI signaling pathway, LUAD

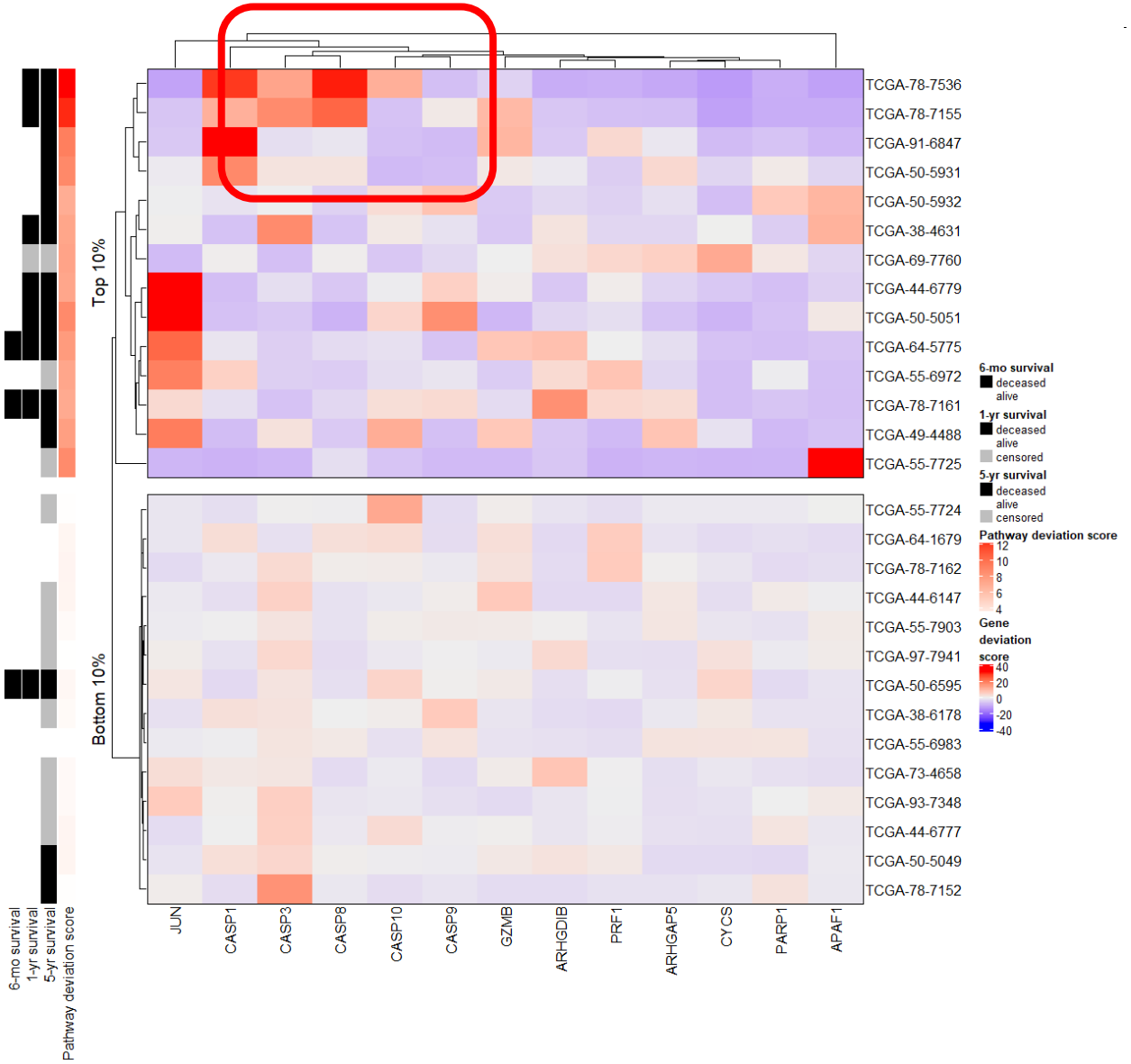






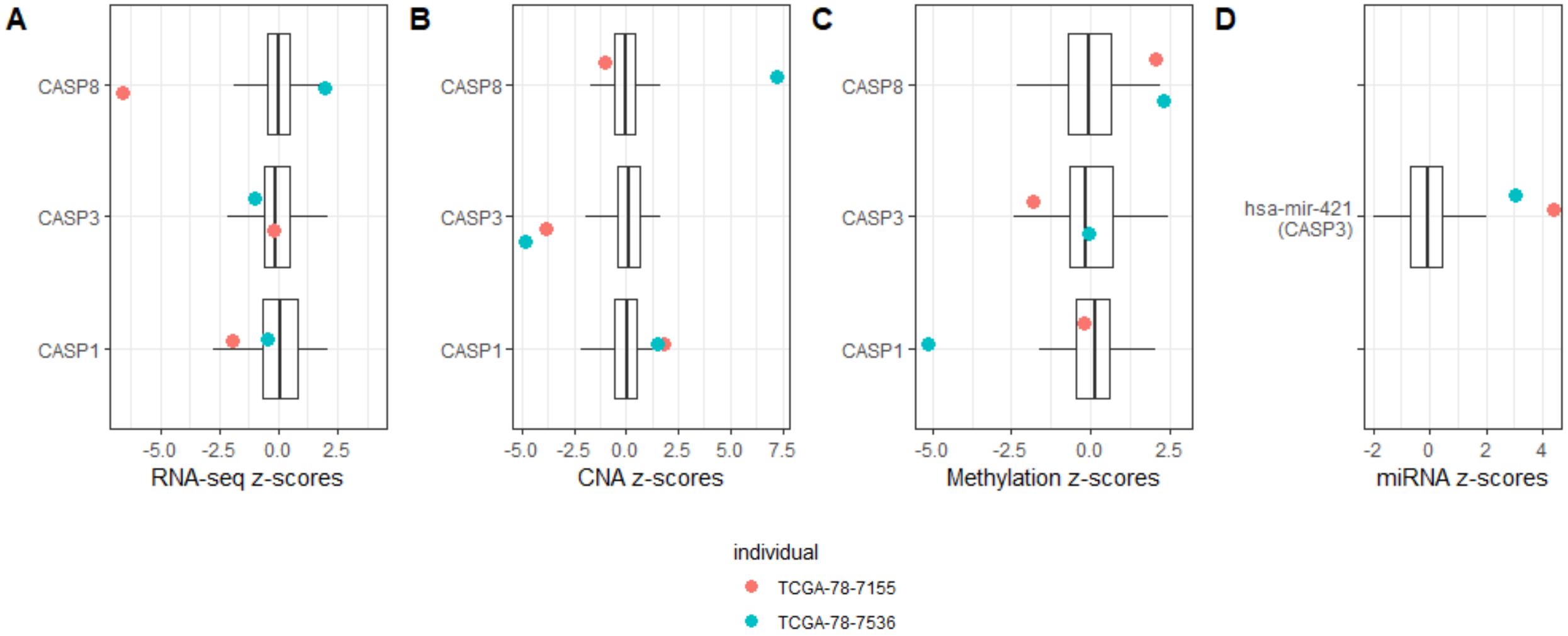
MFA 1: RNA-seq (54.38%)
MFA 2: methylation (42.29%)
MFA 3: CNA (59.18%)

Which genes/omics drive large pathway deviation scores?



→ **CASP1**, **CASP3**, and **CASP8** all have high gene-level deviation scores for the two most extreme individuals…

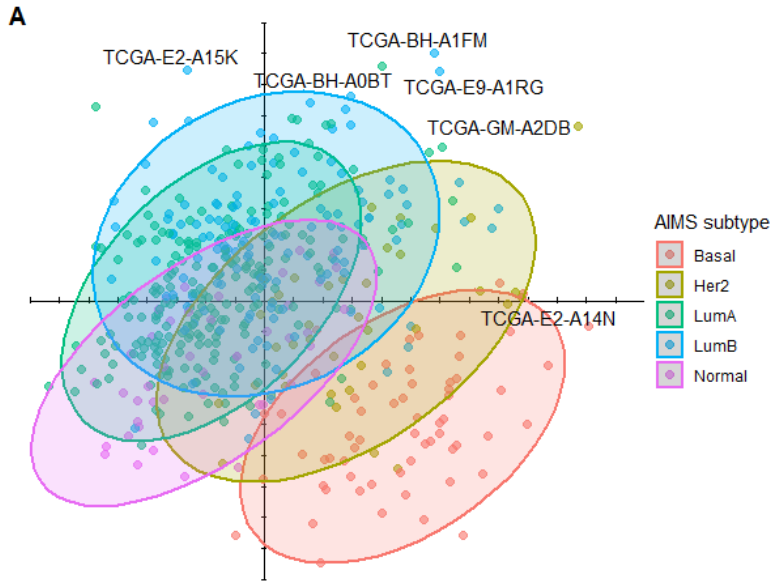
Which genes/omics drive large pathway deviation scores?

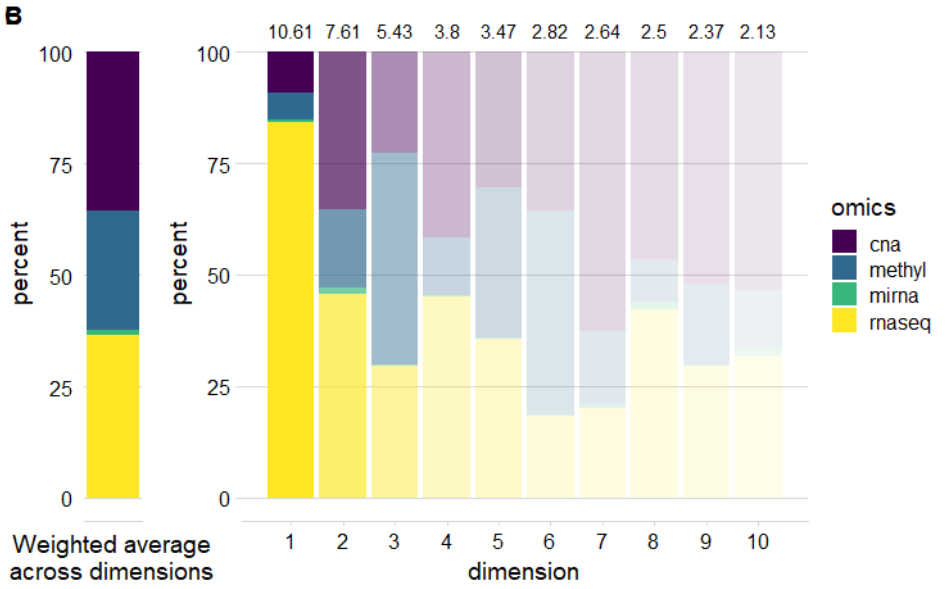


Pathway deviation scores are associated with other clinically relevant phenotypes

- **Nearly all pathways** are associated with two measures of histological grade
- Higher scores = worse outcome

Pathway	Database	Ranking	# of genes
Signaling by Wnt	Reactome	3.16	63
Apoptotic execution phase	Reactome	5.00	52
APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	Reactome	6.78	64
…	…	…	…





* Mitotic index and nuclear pleomorphism (ANOVA, BH padj < 5%)

Pathway deviation variability is associated with BRCA subtype

padma results on TCGA breast and lung cancer

(RNA-seq + miRNA-seq + methylation + CNA data, MSigDB canonical pathways)

- Larger *padma* deviation scores = increasingly aberrant pathway variation with significantly worse prognosis (survival, histological grade) in breast and lung cancer
- Potential outlier detection tool

Innovative use of existing MFA method to calculate and graphically explore individualized multi-omic pathway deviation scores

Future work:

- Potential integration into **Bioconductor** ecosystem (notably, for the *MultiAssayExperiment* class)
- Incorporation of known **hierarchical structure** among genes in pathway
- **Interactivity** for result exploration through an integrated Shiny app
- Extensions for **highly structured data** typical in agronomy (e.g., multi-omic data from divergent chicken lines subject to feed/heat stress or maize diversity panels under control/cold conditions)

Rau et al. (2019) Individualized multi-omic pathway deviation scores using multiple factor analysis. *bioRxiv* https://www.biorxiv.org/content/10.1101/827022v2

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Acknowledgements

AgreenSkills plus
Pathways for inventive researchers
Co-funded by the European Union
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