CLL Genomics

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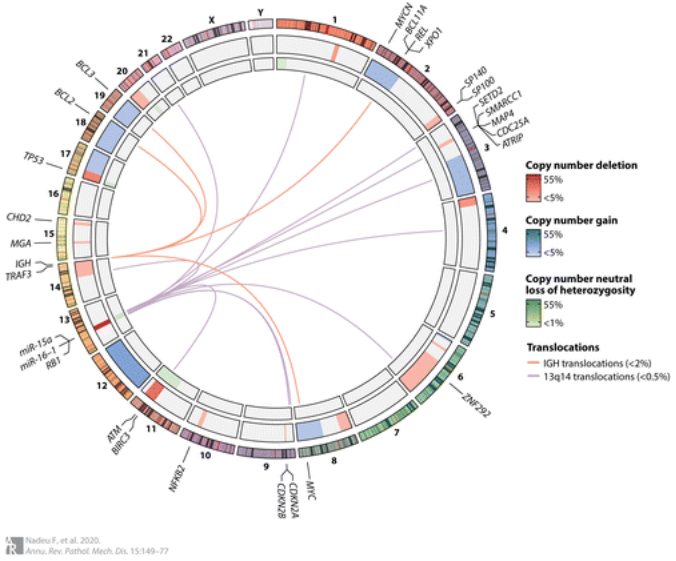
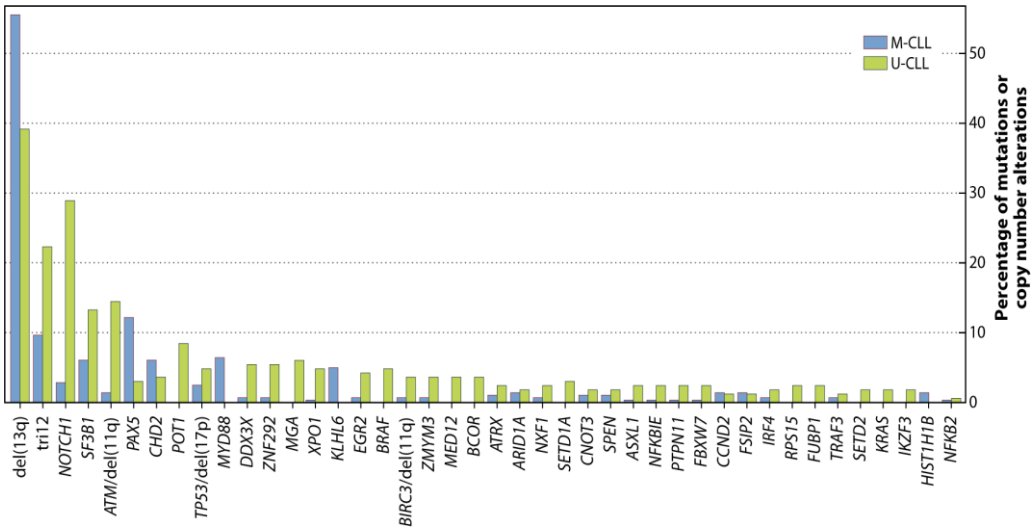
Hospital Clinic, IDIBAPS, University of Barcelona

Disclosures of Elias Campo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda						x	x
NanoString						x	x
Illumina						x	
Janssen							x
EUSPharma							x
Roche							x
GENMAB							x
AstraZeneca	x						
Diagnostica Longwood							x

Genomic Profile of CLL



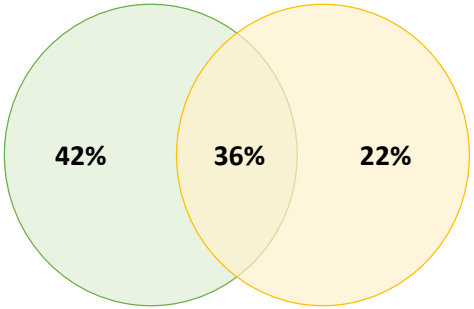


Nadeu F et al , Annu. Rev. Pathol. Mech. Dis. 2020 (Based on Puente et al Nature 2015 and Landau D et al Nature 2015)

The genomic landscape of CLL

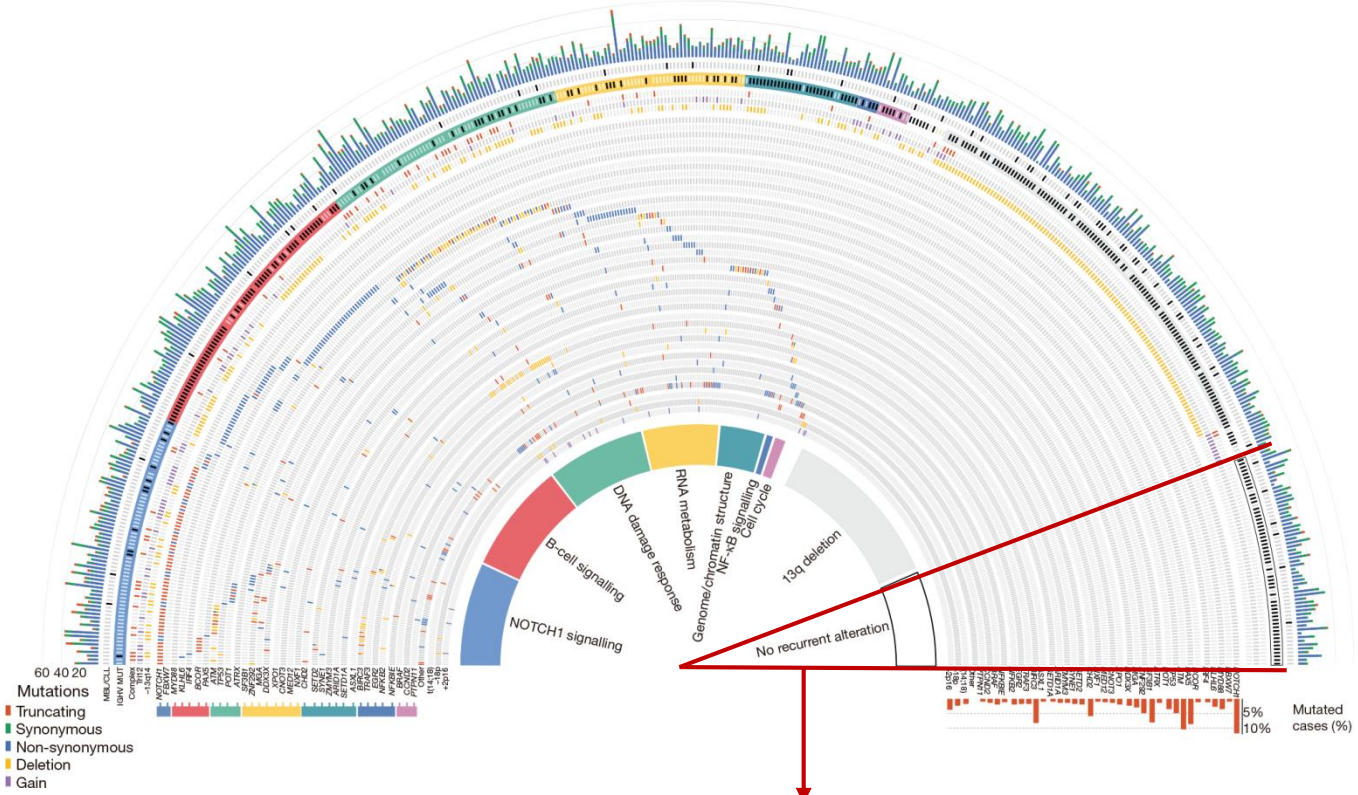
Around 80 potential CLL driver alterations

Puente, Nature 2015 Landau, Nature 2015



Driver discovery might be influenced by:

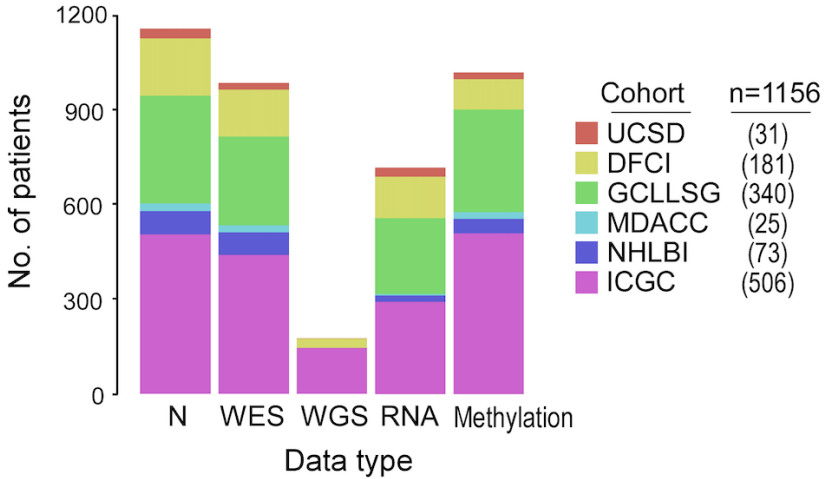
Cohort characteristics
Methodological aspects

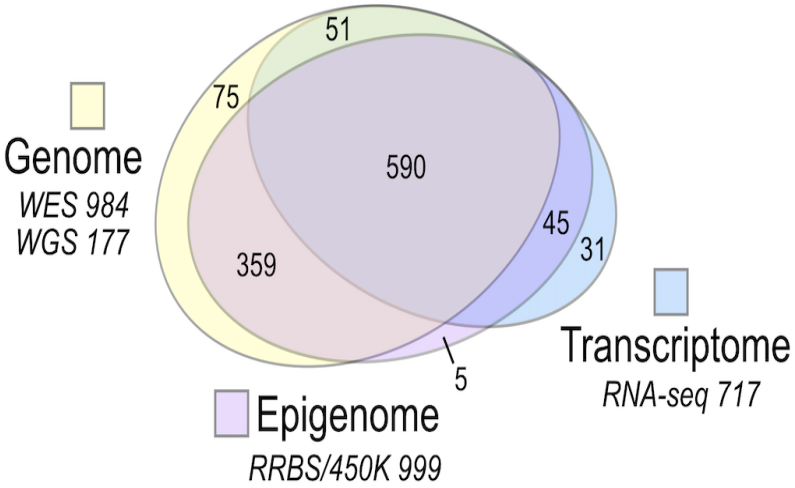


Is the genomic landscape of CLL fully characterized?

Puente XS et al, Nature 2015; Landau DA et al ***Nature*** 2015

CLL-1156 Genome Project



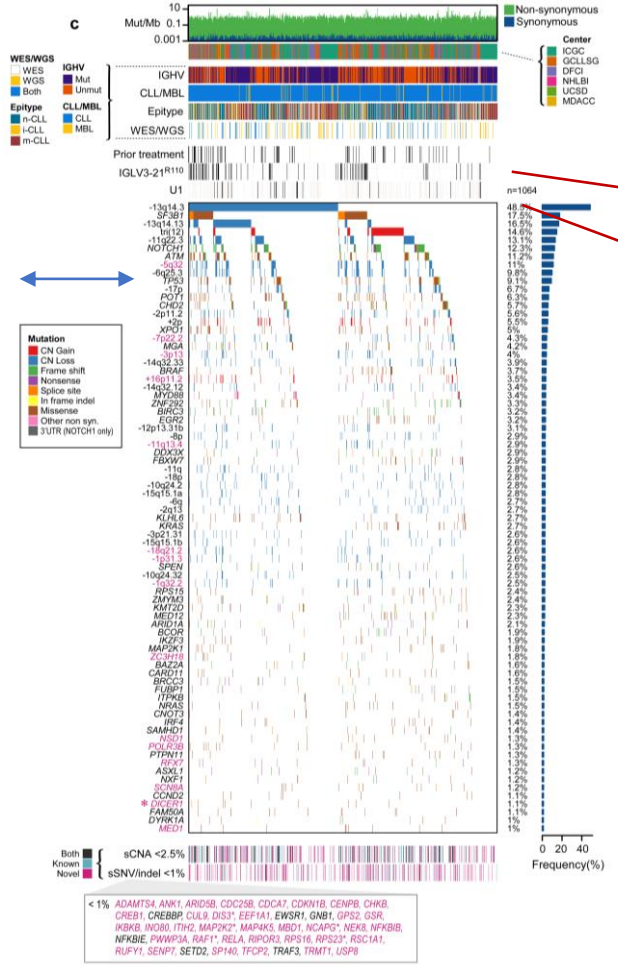


Knisbacher B, Lin Z, Hahn C, Nadeu F, Duran- Ferrer M et al, ***Nat Genetics*** 2022

Towards a complete characterization of the genetic drivers of CLL

SF3B1
NOTCH1
ATM
TP53

POT1
XPO1
MGA
BRAF
MYD88
BIRC3

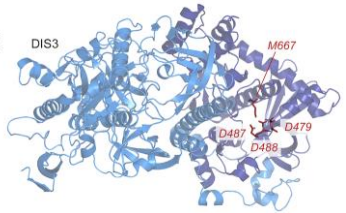


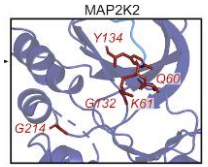
2 driver genes identified in complex o repetitive regions of the genome

IGLV3-21^{R110} 9.4%

U1 g.3A>C 3.9%

6 additional driver genes identified through spatial clustering of mutations in 3-D protein structure

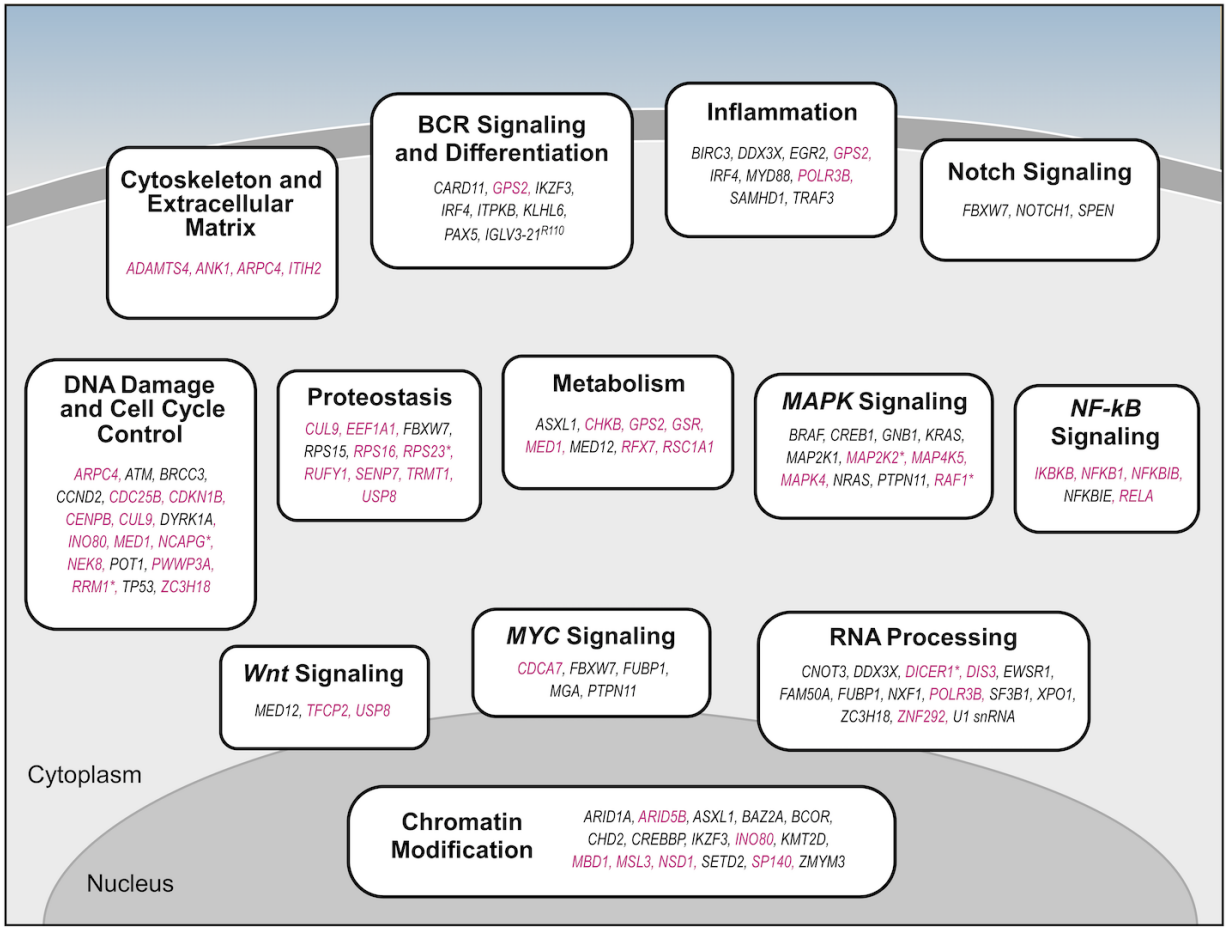




- **82 putative CLL driver genes (37 novel)**
- **59/82 in <2% of patients**
- **Novel driver gene is the sole mutation in 4%**
- **3.8% driver-less patients [6.6% in M-CLL, 0.6% in U-CLL]**

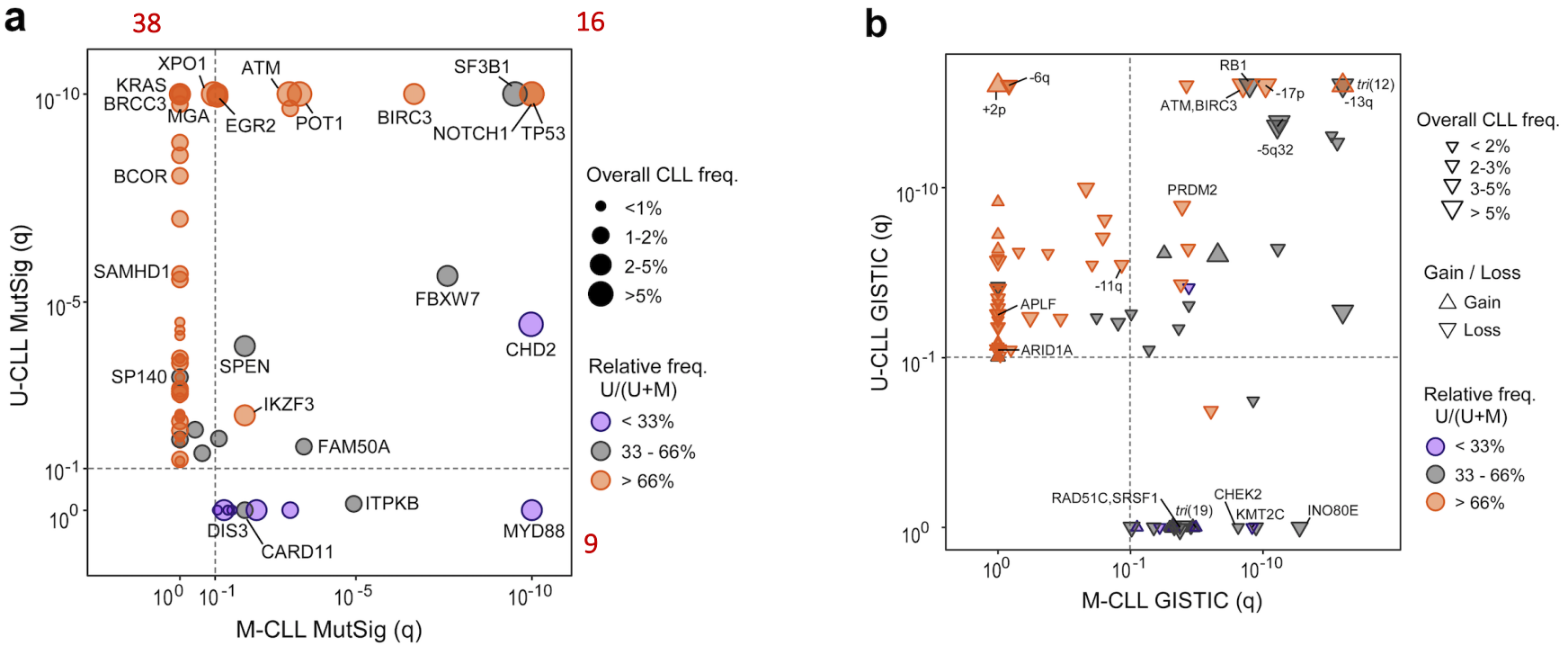
Knisbacher B, Lin Z, Hahn C, Nadeu F, Duran- Ferrer M et al, ***Nat Genetics*** 2022

Biological pathways affected by driver alterations



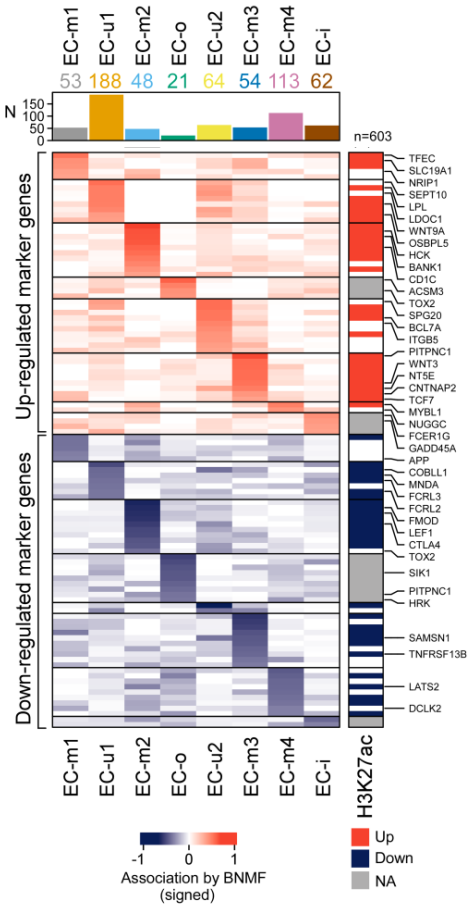
Knisbacher B, Lin Z, Hahn C, Nadeu F, Duran- Ferrer M et al, *Nat Genetics* 2022

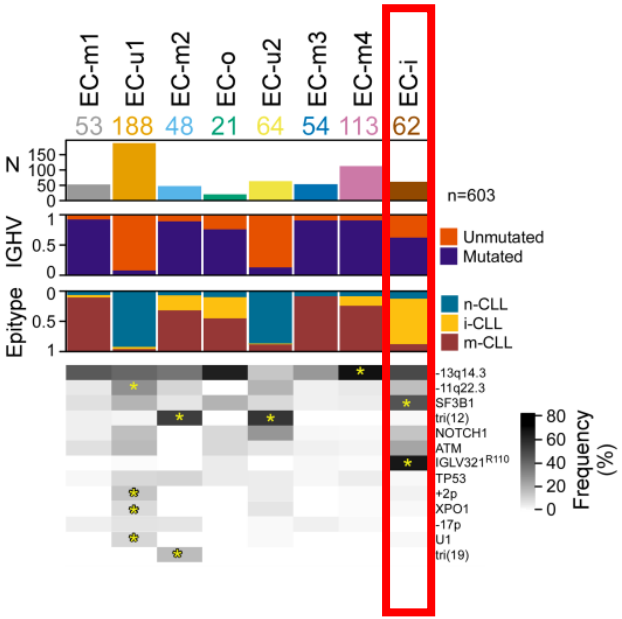
Driver alterations in IGHV subtypes

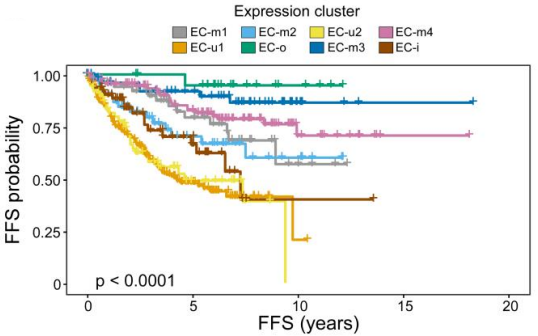


Knisbacher B, Lin Z, Hahn C, Nadeu F, Duran- Ferrer M et al, *Nat Genetics* 2022

CLL Transcriptomic clusters







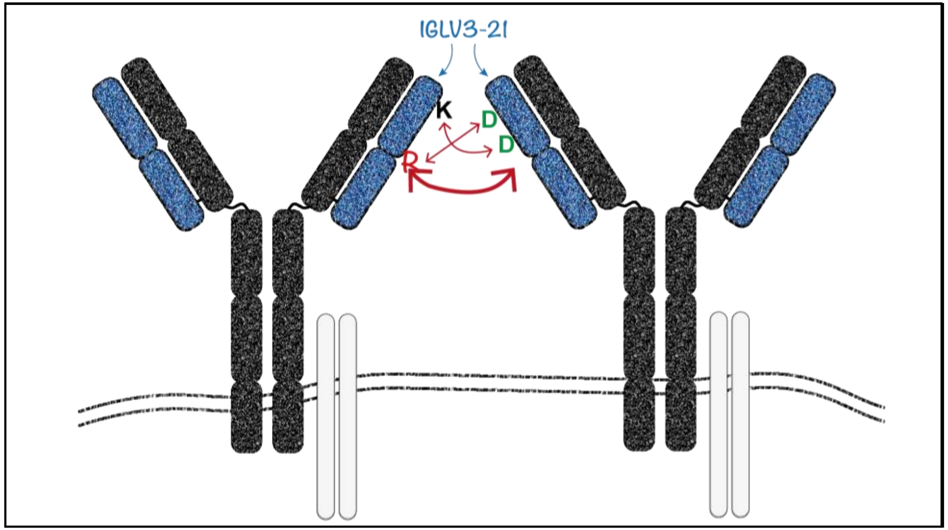
FFS without blacklisted participants, n=603

EC-m1	53	28	3	0	0
EC-u1	188	43	1	0	0
EC-m2	48	20	6	0	0
EC-o	21	18	4	0	0
EC-u2	64	13	0	0	0
EC-m3	54	38	3	1	0
EC-m4	113	68	13	1	0
EC-i	62	17	1	0	0

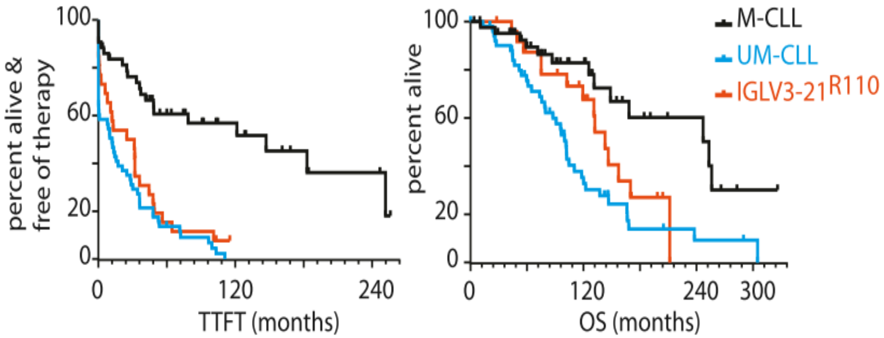
Knisbacher B, Lin Z, Hahn C, Nadeu F, Duran- Ferrer M et al, ***Nat Genetics*** 2022

Beyond IGHV mutational status: IGLV3-21^{R110}

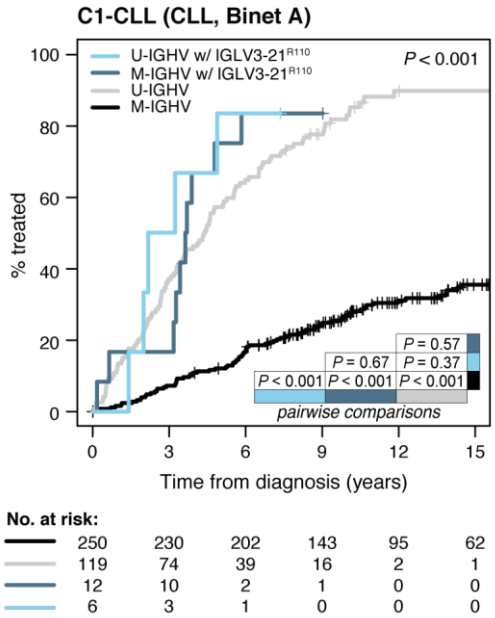
- 8-18% of cases carrying the IGLV3-21^{R110}.
- **50% M-IGHV, 50% U-IGHV**
- All subset #2 carried the IGLV3-21^{R110},
- But subset #2 represented a minority of the IGLV3-21^{R110} cases.
- Poor outcome

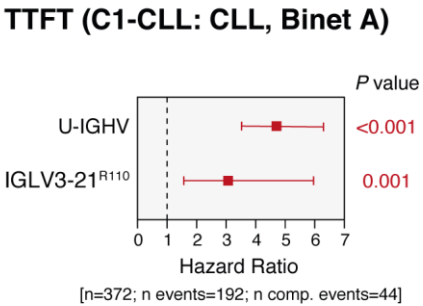


Minici, Nat Commun 2017 [drawing based on Maity, PNAS 2020]
Dühren-von Minden M, Nature 2012



IGVL3-21 ^{R110} CLL has a clinical evolution similar to IGHV-unmutated independently of the IGHV mutational status

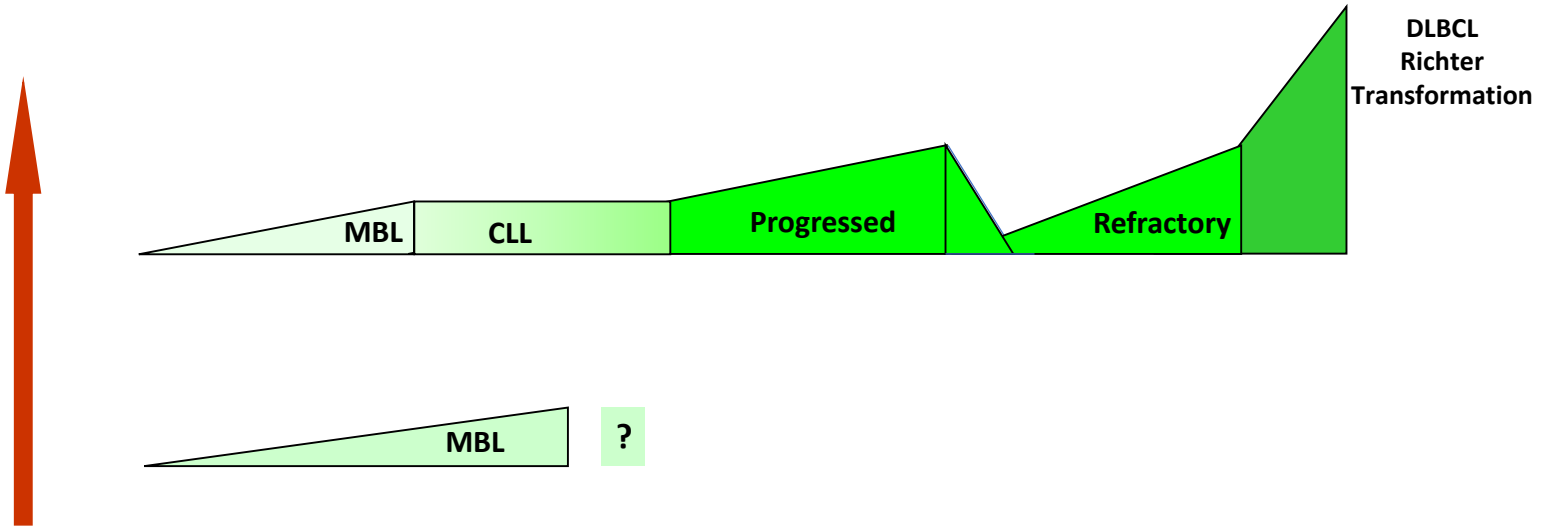


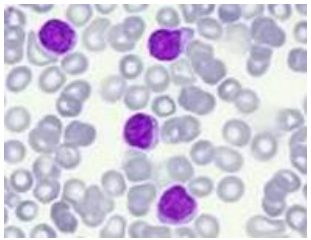


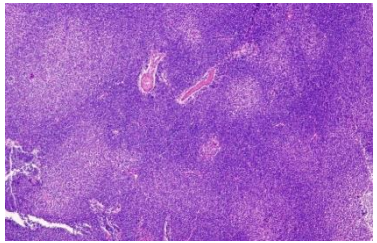
Nadeu F et al Blood 2020

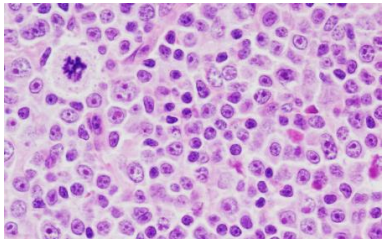
Disease Progression in CLL

Clonal B-cell selection and expansion

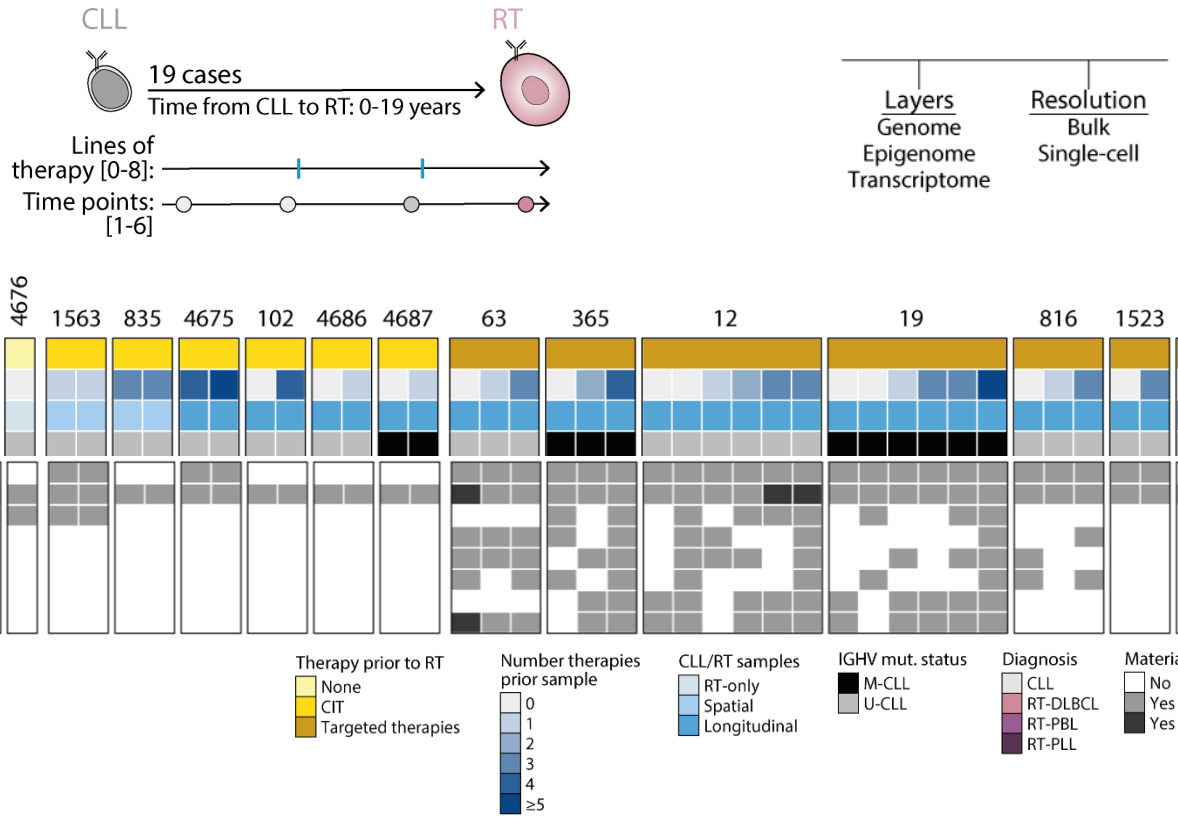






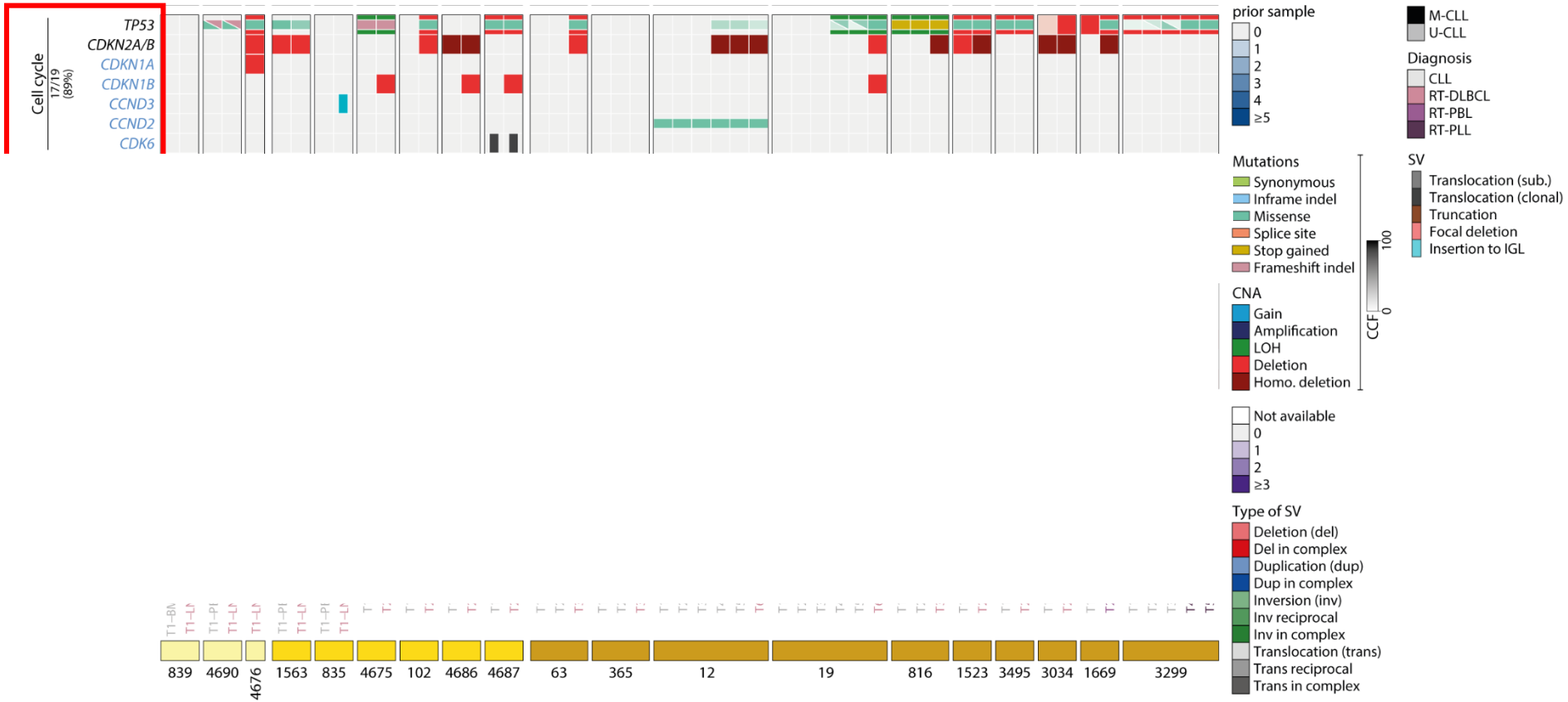


What are the genomic mechanisms leading to Richter Transformation in CLL?



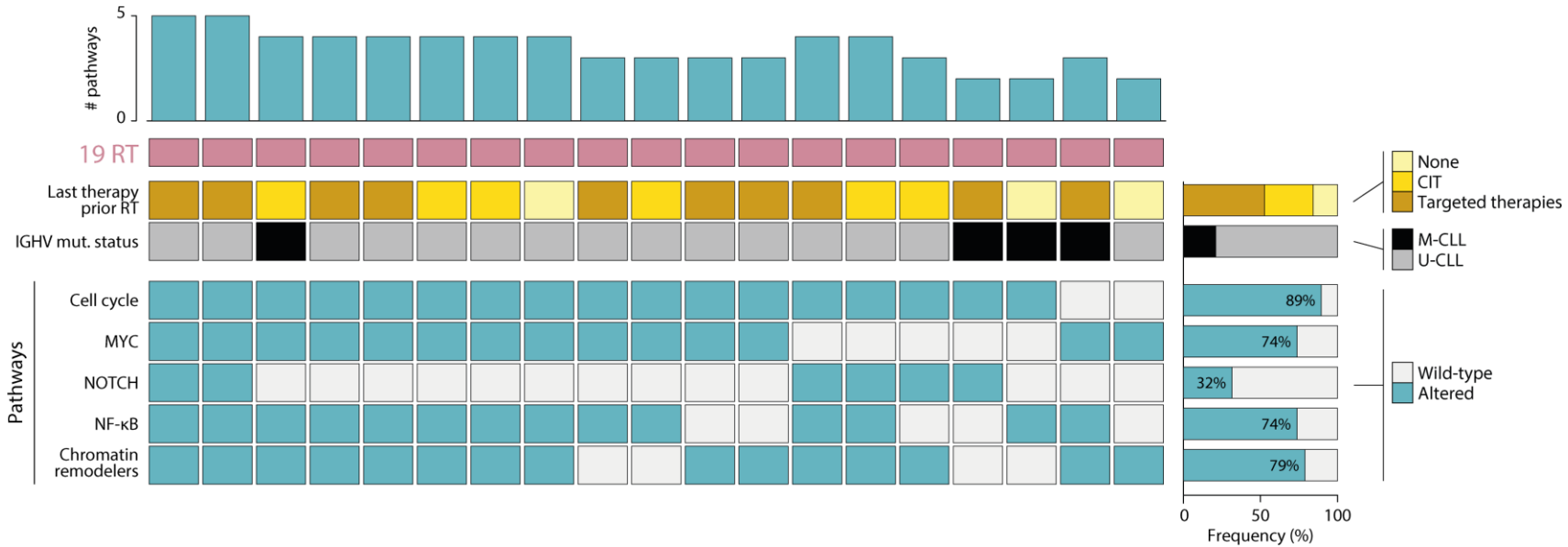
Nadeu F, Royo R, et al, Massoni-Badosa R, Playa-Albinyana H, Garcia B et al *Nat Medicine* 2022 In press

Similar chromosomal landscape of RT after different treatment modalities



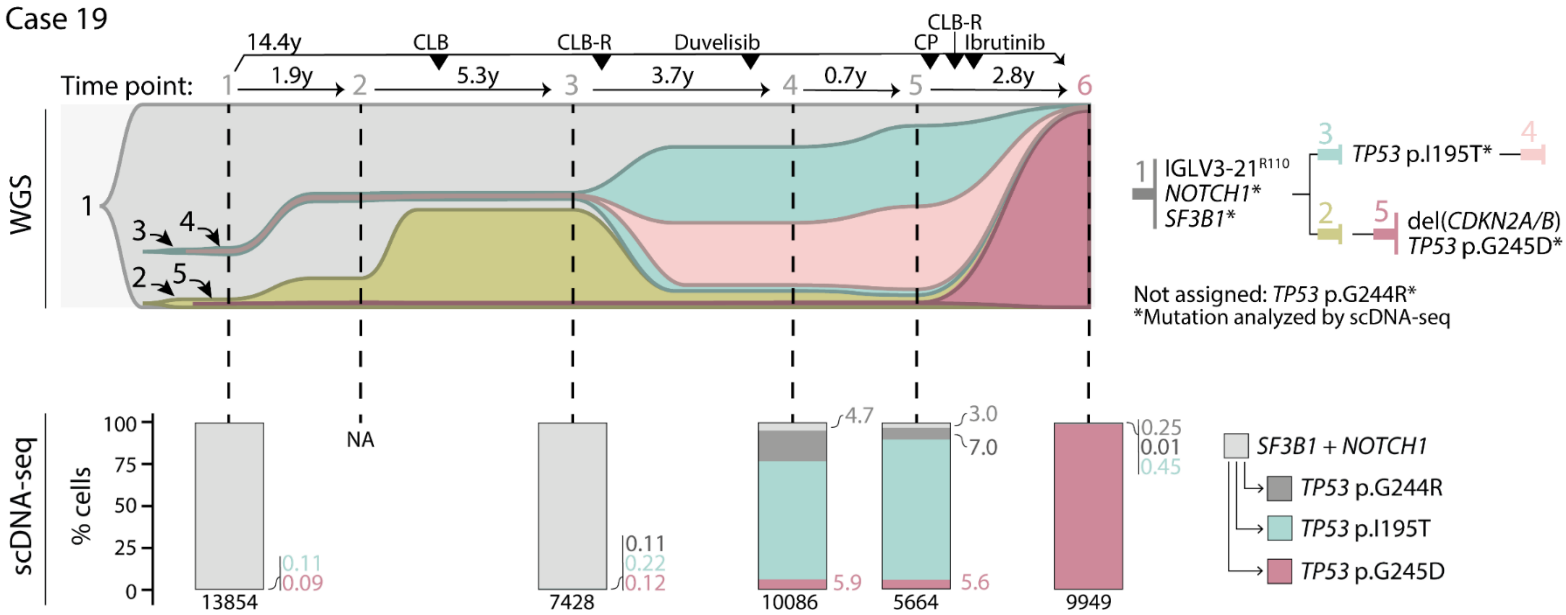
Nadeu et al. *Nat Medicine* 2022; 28(8):1662-1671

Pathways Genetically Altered in RT



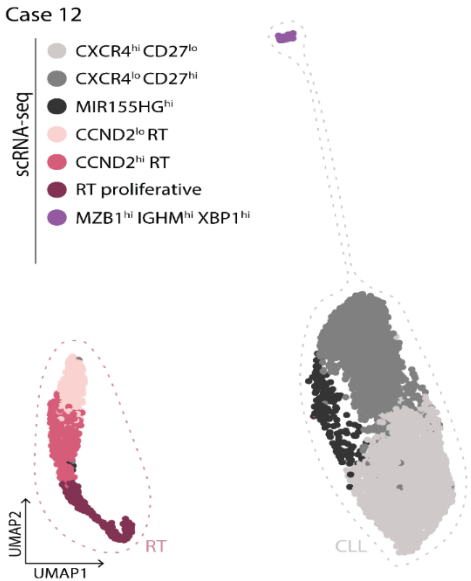
Nadeu et al. ***Nat Medicine*** 2022; 28(8):1662-1671

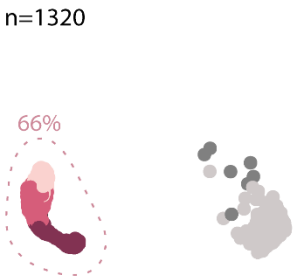
Early seeding of RT: tracking driver mutations by scDNA-seq



Nadeu et al. *Nat Medicine* 2022; 28(8):1662-1671

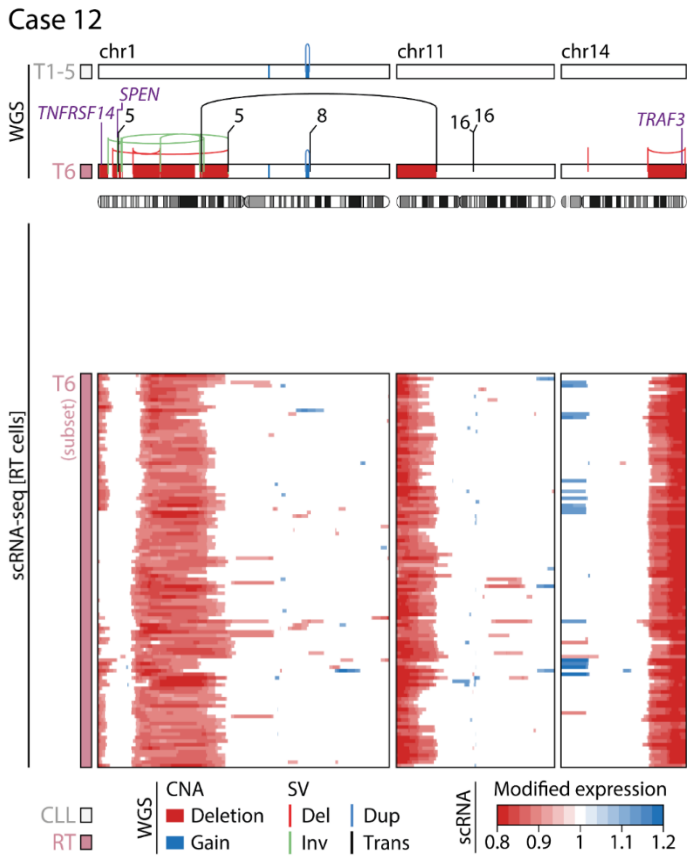
Single cell analysis detects early seeding of subclonal relapses and transformation in CLL





Nadeu et al. *Nat Medicine* 2022; 28(8):1662-1671

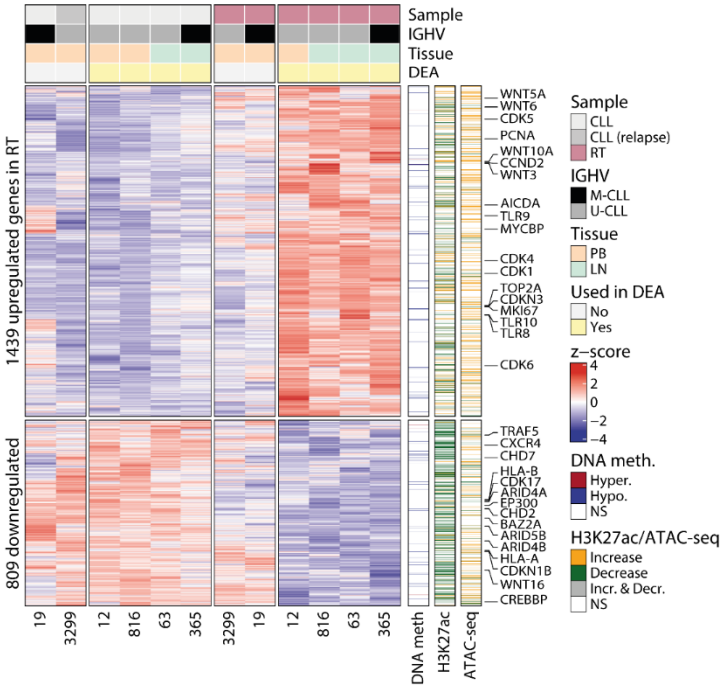
Early seeding of RT: linking genomics and transcriptomics in RT seeds

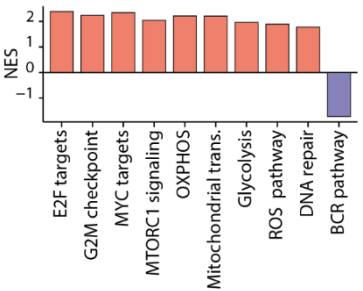


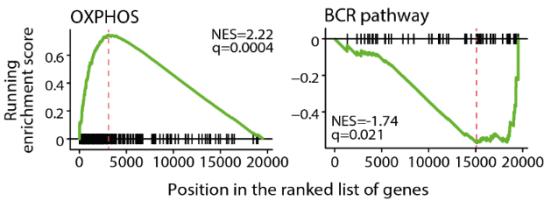
RT: Richter transformation

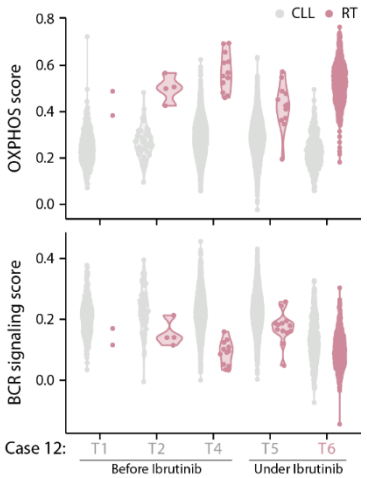
Nadeu et al. ***Nat Medicine*** **2022; 28(8):1662-1671**

The OXPHOS^{high}-BCR^{low} transcriptional axis of RT









This axis might explain the selection and rapid expansion of small RT subclones under therapy with BCR inhibitors

Monti Blood 2005; Caro Cancer Cell 2012; Norberg Cell Death Differ 2017.

RT: Richter transformation; BCR: B-cell receptor

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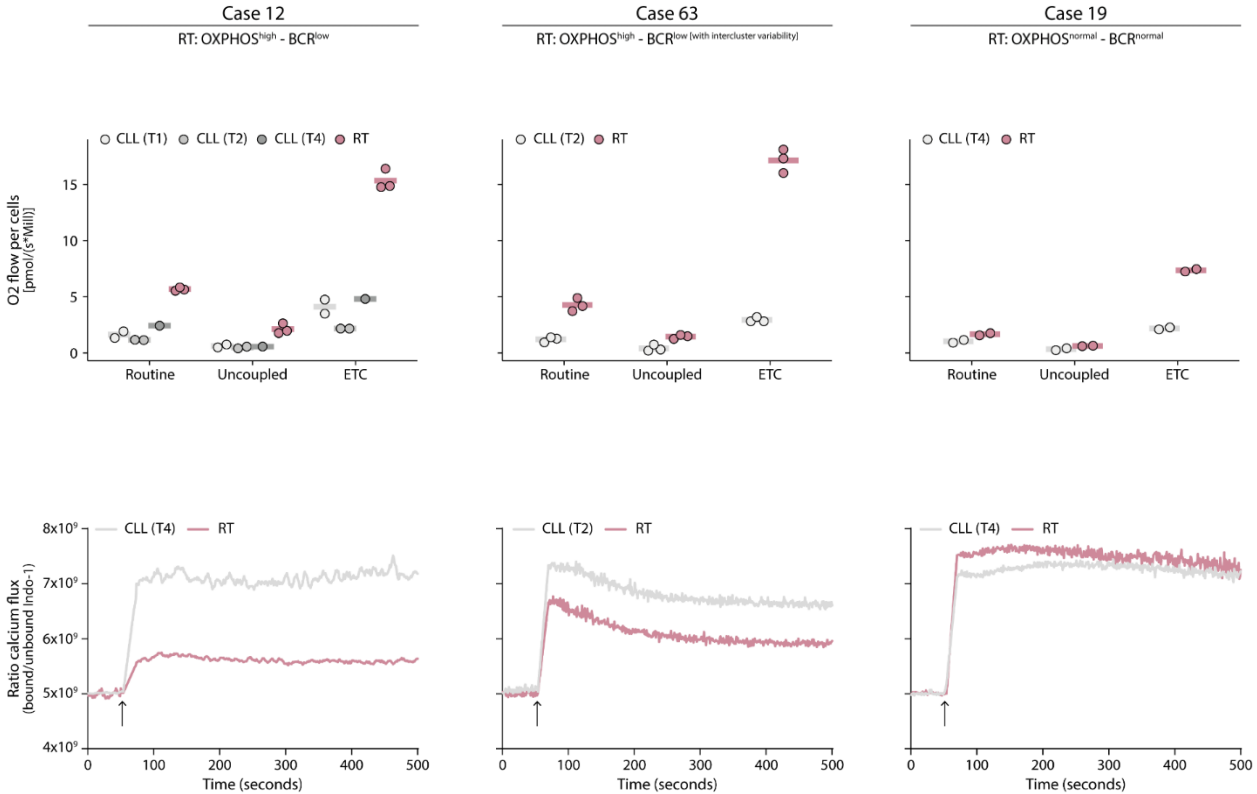
Cellular respiration and BCR signaling in RT cells





RT: Richter transformation; BCR: B-cell receptor

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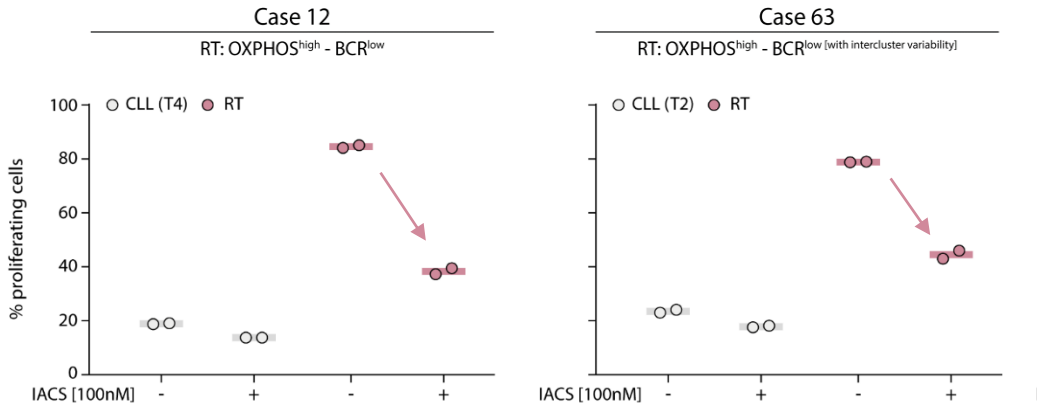
The OXPHOS^{high} phenotype of RT is of potential therapeutic value

OXPHOS pathway can be exploited therapeutically.

Caro Cancer Cell 2012; Norberg Cell Death Differ 2017; Molina Nat Med 2018;
Vangapandu Oncotarget 2018; Zhang Sci Transl Med 2019; Ravera Sci Rep 2020; Chen Nat Commun 2021.



RT: Richter transformation

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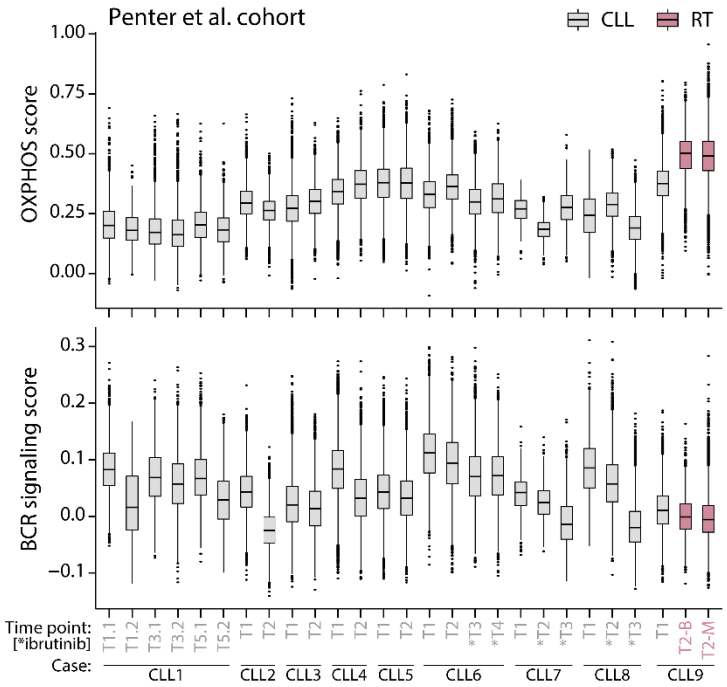
Validation in an independent CLL/RT cohort



Penter et al Cancer Discov 2021

Conclusions

- The CLL genomic map is virtually complete and reveals a very heterogeneous landscape with relevant driver in small subsets and specific alterations in IGHV subtypes
- Transcriptome profiles identifies different CLL subtypes associated with different IGHV subtypes and mutational profile (IGVL3-21 R110)
- RT-cells with fully-assembled genomic, immunogenetic, and transcriptomic profiles may already be present at CLL diagnosis 6-19 years before the clonal explosion associated with the clinical transformation
- The transcriptome of RT converge into an $OXPHOS^{high}$-BCR^{low} axis of potential therapeutic value.

RT: Richter transformation

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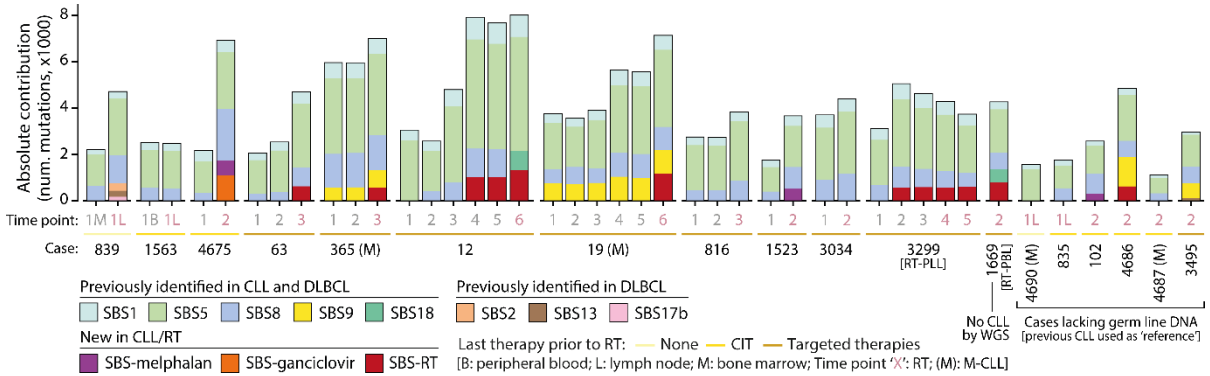
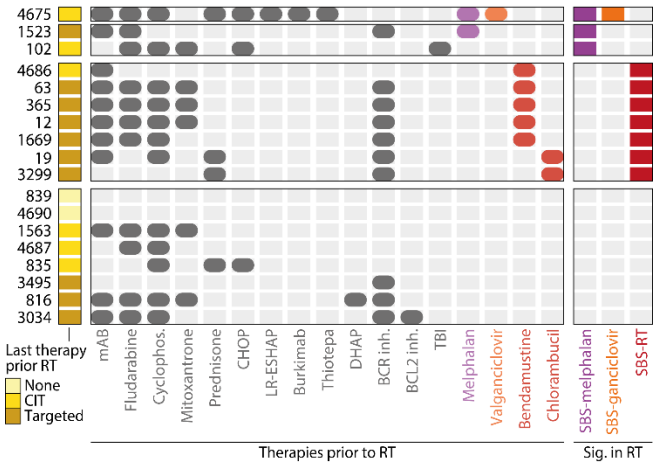
Thank you!

Footprints of cancer therapies in RT





Nadeu et al. *Nat Medicine* 2022; 28(8):1662-1671