Impatto clinico dell'analisi multiomica nelle MDS

Gabriele Todisco
Leukemia Unit, Humanitas Cancer Center, Milan, Italy
Center for Accelerating Leukemia/Lymphoma Research (CALR), Humanitas University, Milan, Italy

Outline

1. **Multi-omic approach - Definizione**

2. **MDS con sideroblasti ad anello**

3. **VEXAS syndrome**

Multi-omic approach

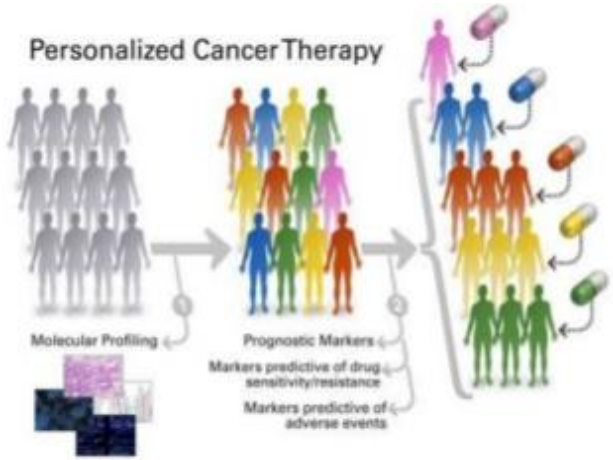
High-throughput sequencing methods

DNA-seq

RNA-seq

Dati Clinici

Follow-up prospettico



~ 100 variabili continue

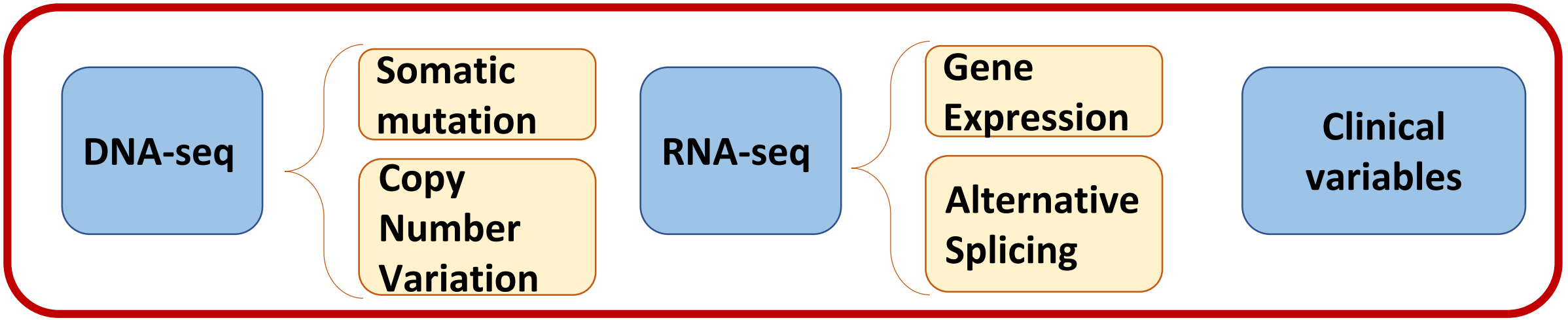
~ 15000 variabili continue

~ 50 variabili continue

~ 20 variabili continue

Personalized medicine

Multi-omic approach



MAIN AIM: to establish a multidimensional resource for multiomics data integration

1. **Explorative approach → Hypothesis generation**
2. **Confirmatory approach → Results validation**

Genomic-Transcriptomic Landscape of MDS with RS

BACKGROUNG

- **Ring sideroblasts** (RS) → Marker of erythroid displasia
  - MDS-RS-SLD/MLD (usually SF3B1-mutated)
  - higher-risk MDS, MPN, MDS/MPN and AML

- 20% of MDS with RS (MDS^{RS+}) cases carries no SF3B1 mutation, suggesting that different molecular mechanisms may underlie RS formation.

- Little is known about the molecular pathophysiology of *SF3B1*-unmutated MDS-RS-SLD/MLD

Genomic-Transcriptomic Landscape of MDS with RS

AIMS

- To provide a comprehensive evaluation of combined genomic/transcriptomic profiles in MDS with RS

- To characterize the relationships between genomic/transcriptomic profiles, disease phenotype and clinical outcome

Genomic-Transcriptomic Landscape of MDS with RS

Patients' population

- **Patient referred to KI MDS BB between 2004 to 2020**

847 MDS confirmed cases (not previously treated, confirmed diagnosis)

129 MDS cases with RS > 5%

Clin Cancer Res 2023;29(20):4256-4267

Genomic-Transcriptomic Landscape of MDS with RS

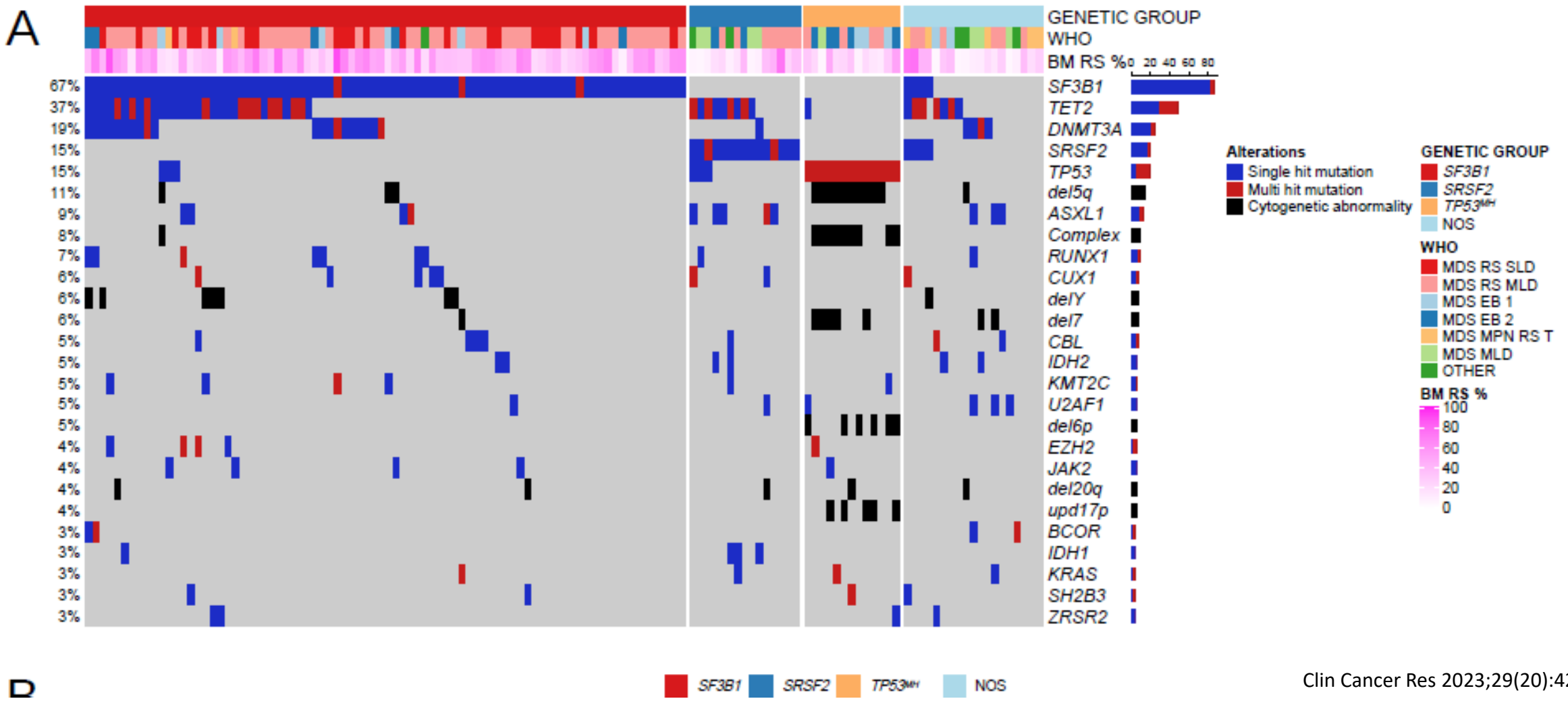
Methods

- **Clinical metadata on prospective cohort with 16 years follow-up**
- **Targeted DNAseq on MNC (162 genes + CNV on tumor cells)**
- **Whole transcriptome (RNASeq) on ~ HSPC (CD34+ bone marrow MNC)**

Clin Cancer Res 2023;29(20):4256-4267

Genomic-Transcriptomic Landscape of MDS with RS

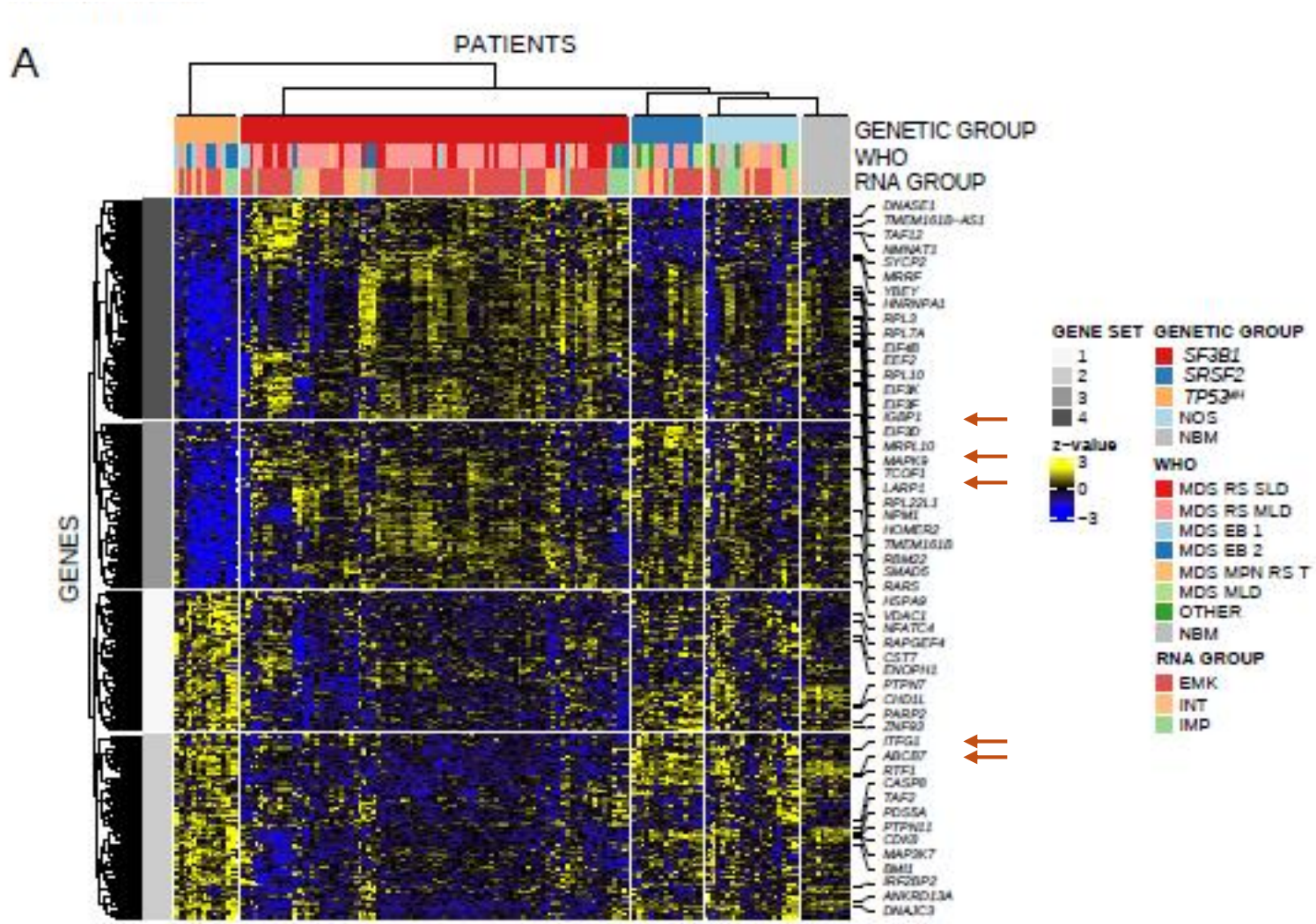
MUTATIONAL LANDSCAPE OF MDSRS+



Clin Cancer Res 2023;29(20):4256-4267

Genomic-Transcriptomic Landscape of MDS with RS

Differential gene expression analysis revealed distinct signatures among *SF3B1*, *SRSF2* and *TP53*^{MH} mutated MDS^{RS+}

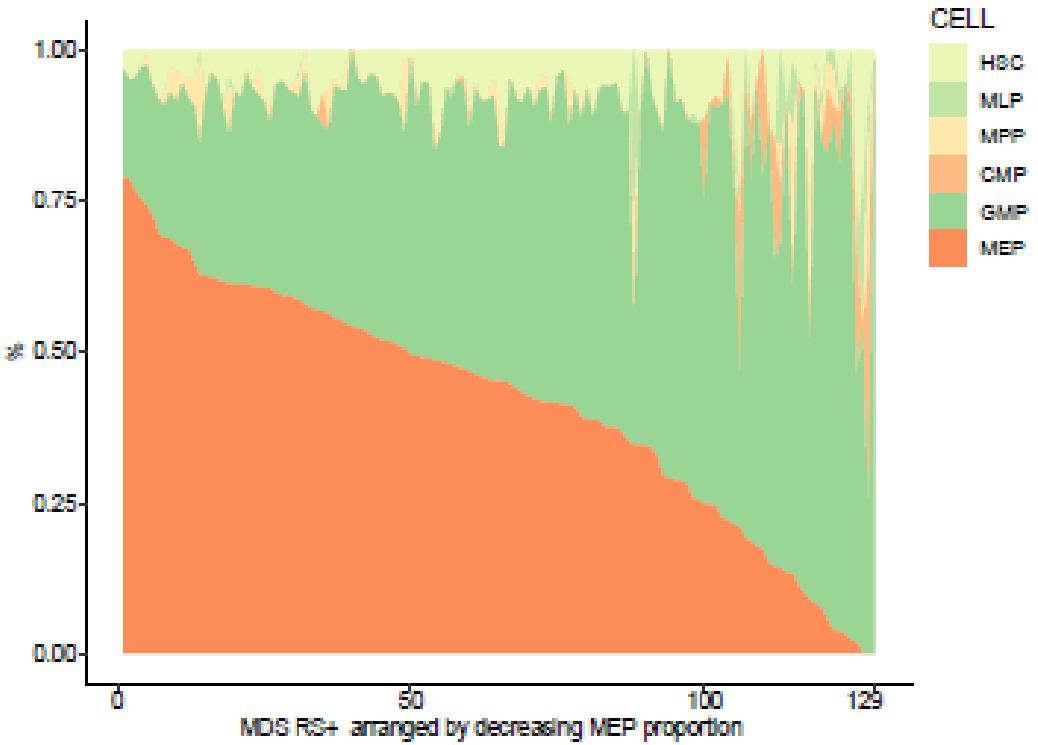


Clin Cancer Res 2023;29(20):4256-4267

TRANSCRIPTOME REFLECTS HSPC DISTIBUTION

We hypothesized that the CD34^{+} MNC transcriptome may reflects composition in hemopoietic stem and progenitor cells (HSPC).

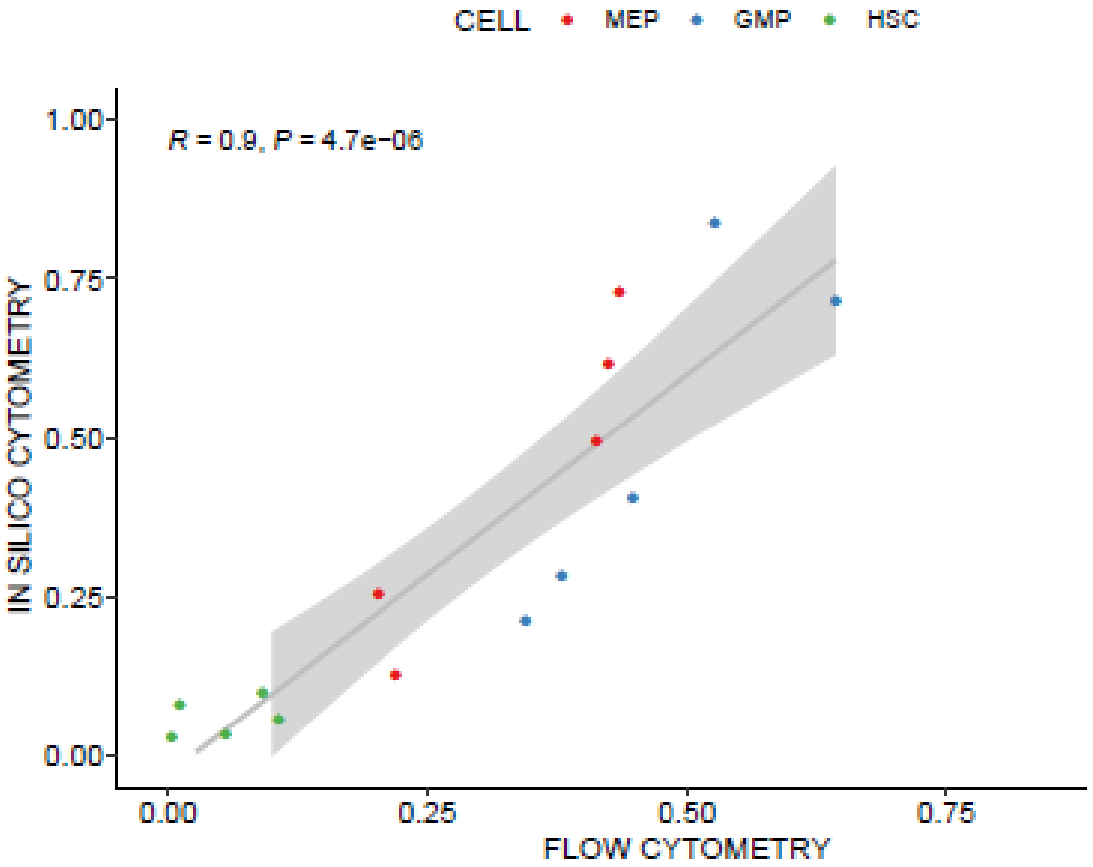
To explore this hypothesis, we used single cell transcriptomic-based deconvolution to dissect distinct HSPCs in the CD34^{+} BM MNC transcriptome.



Clin Cancer Res 2023;29(20):4256-4267

TRANSCRIPTOME REFLECTS HSPC DISTIBUTION

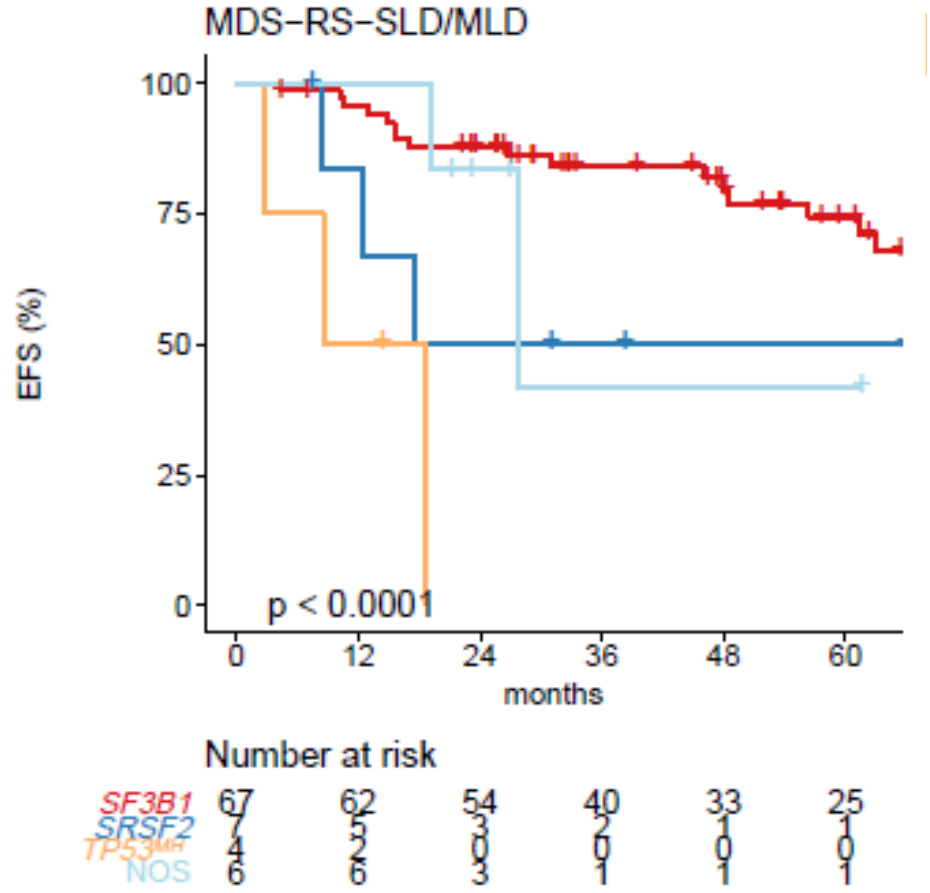
Results from RNA deconvolution were validated using multiparameter flow cytometry (R=0.9, *P* 0.0001) in a subset of 5 cases already included into this study.

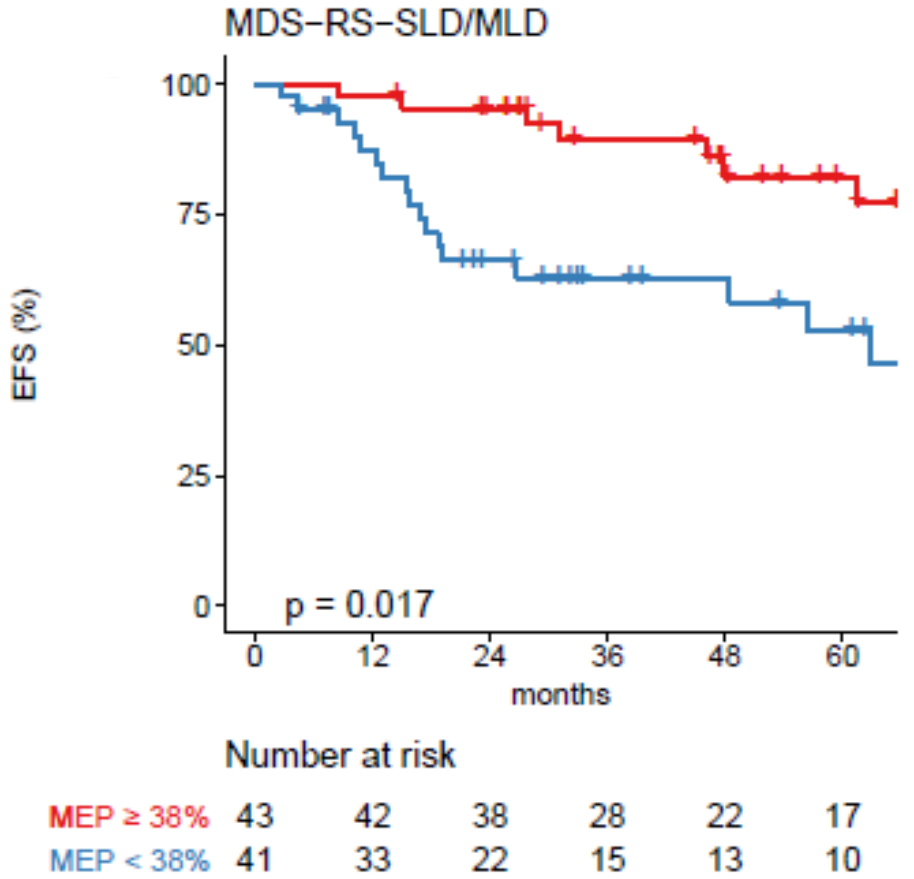


Clin Cancer Res 2023;29(20):4256-4267

Genomic-Transcriptomic Landscape of MDS with RS

Survival analysis



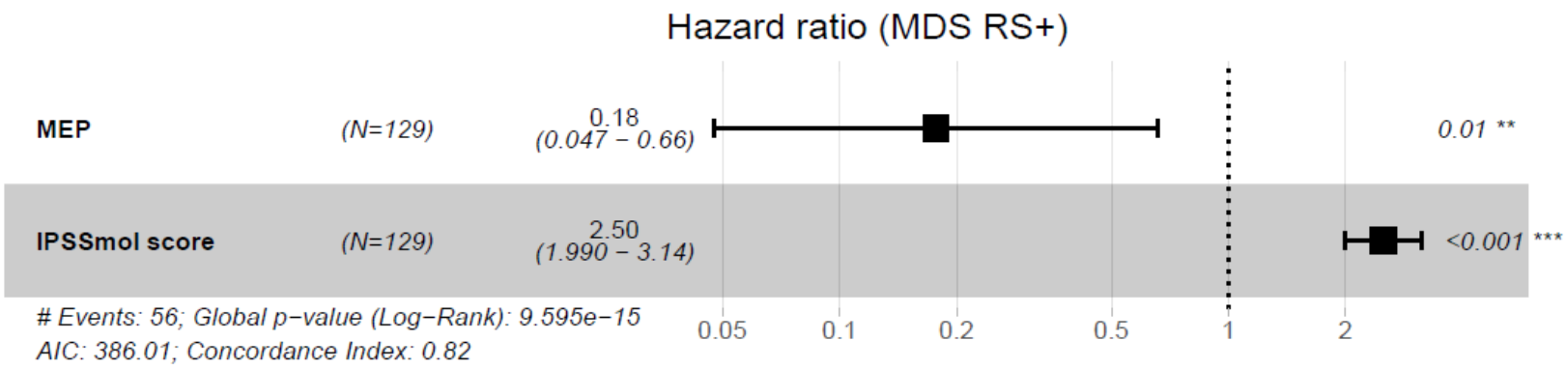


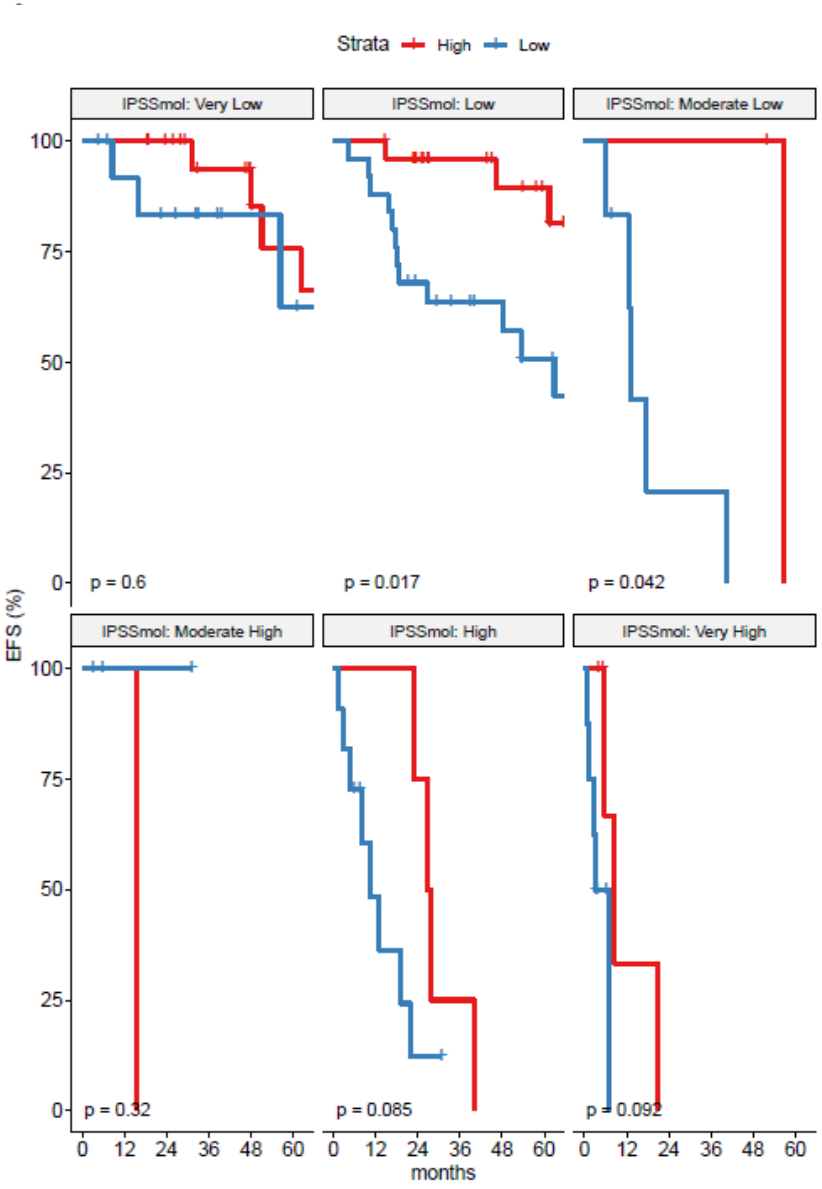
Clin Cancer Res 2023;29(20):4256-4267

Genomic-Transcriptomic Landscape of MDS with RS

Survival analysis

Risk stratification based on MEP signature can improve prognosis stratification based on IPSS-mol (current gold-standard in MDS)





Genomic-Transcriptomic Landscape of MDS with RS

Multi-omic approach confirmed that:

MDS-RS need to be classified according to their genomic driver, irrespective of RS %

Transcriptomic profiles differ according to the genetic driver

Megakariocyte/Erythroid Precursors BM quantification can improve IPSS-mol performace in low-moderate risk

New tests can be developed to predict treatment responsce (flow cytometry / nanostring)

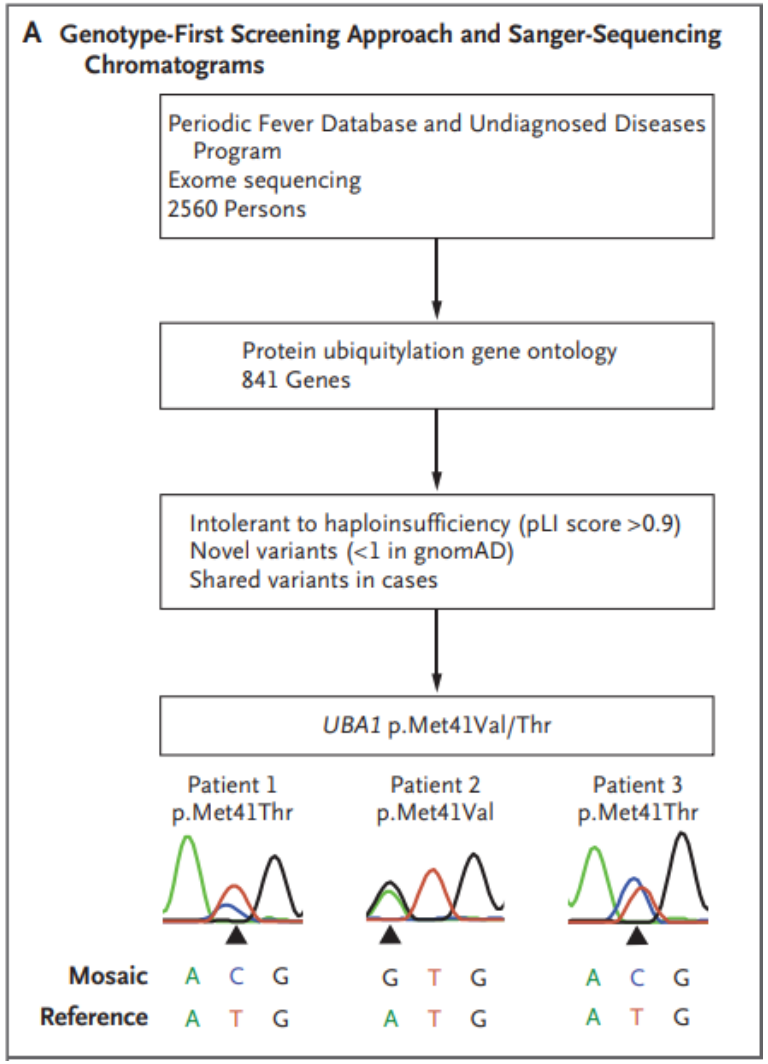
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease

Beck D et al, N Engl J Med 2020;383:2628-38.

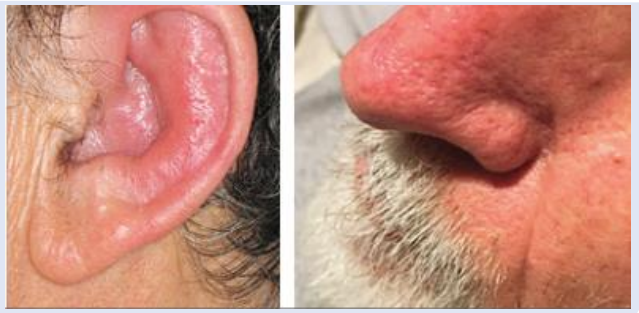
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

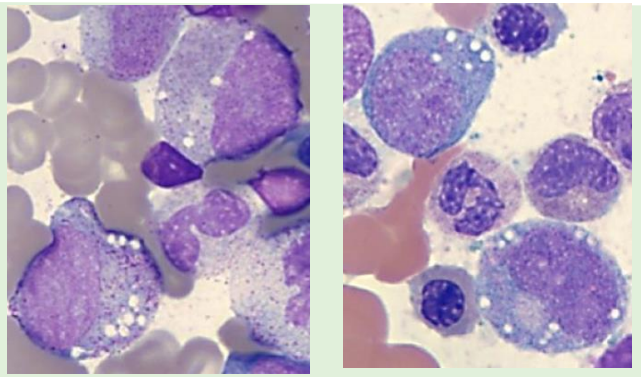
Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease

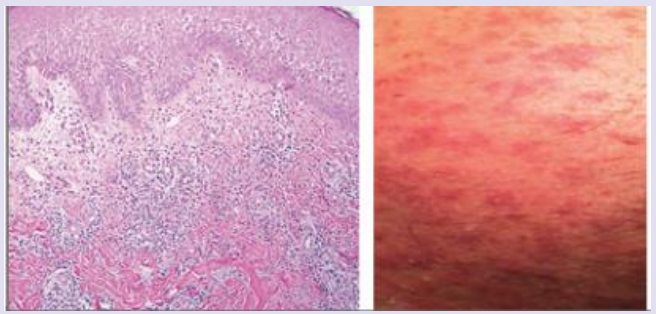


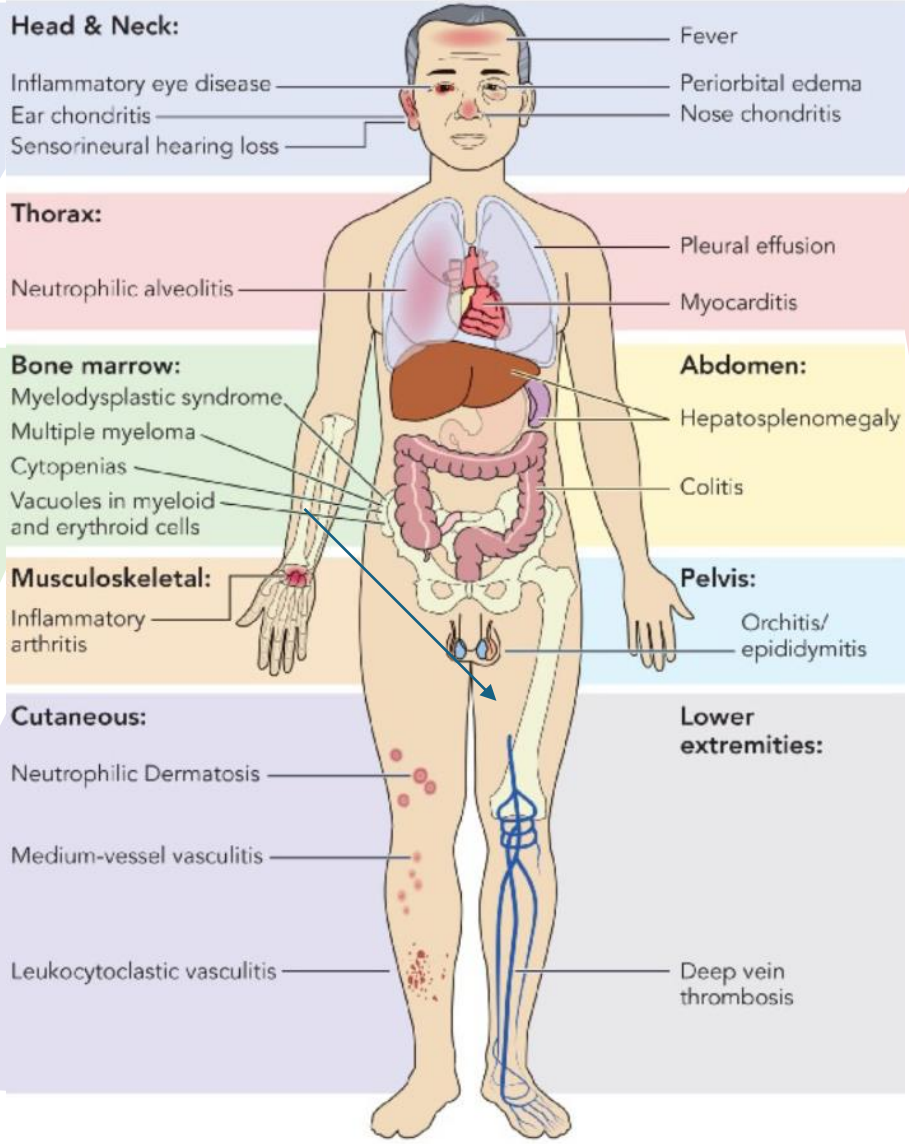
Beck D et al, N Engl J Med 2020;383:2628-38.

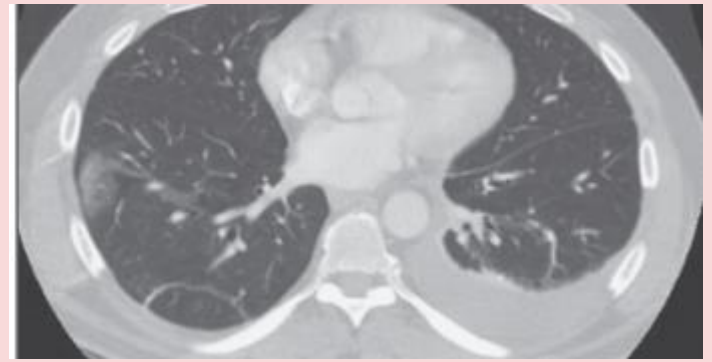
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

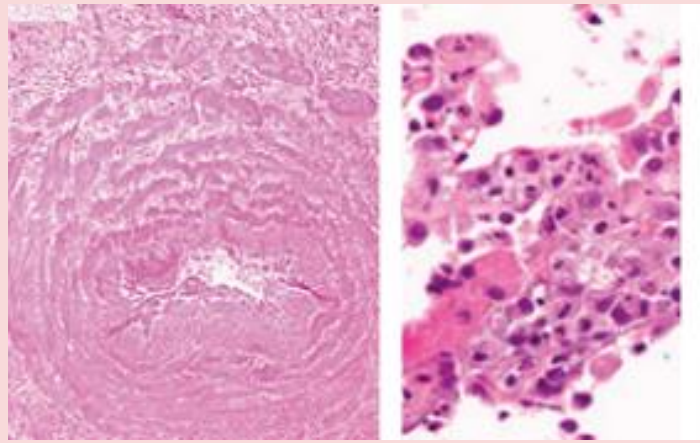








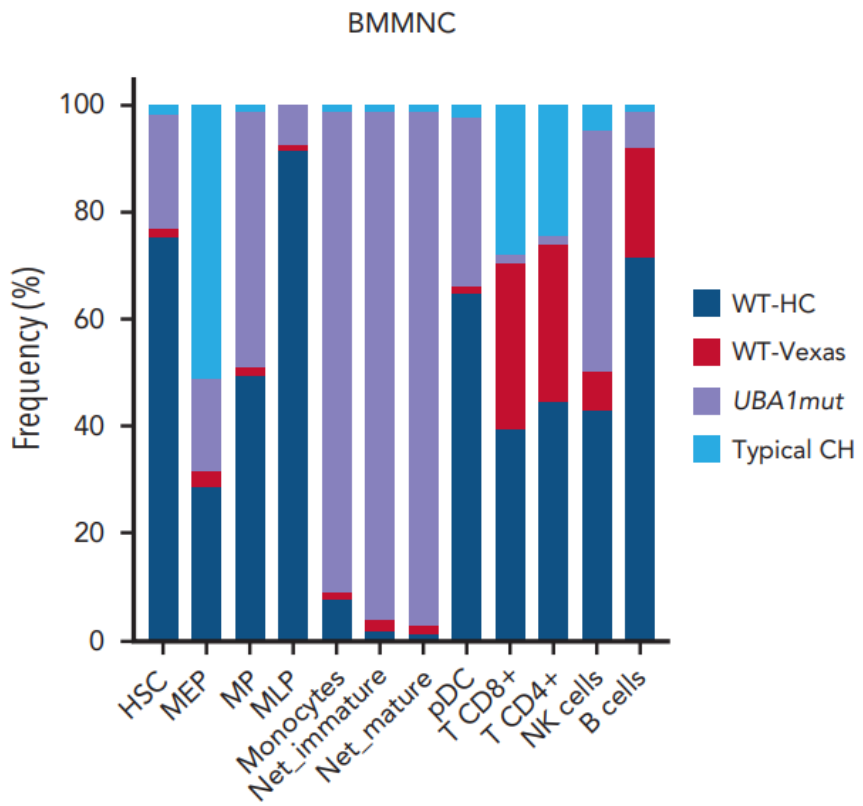


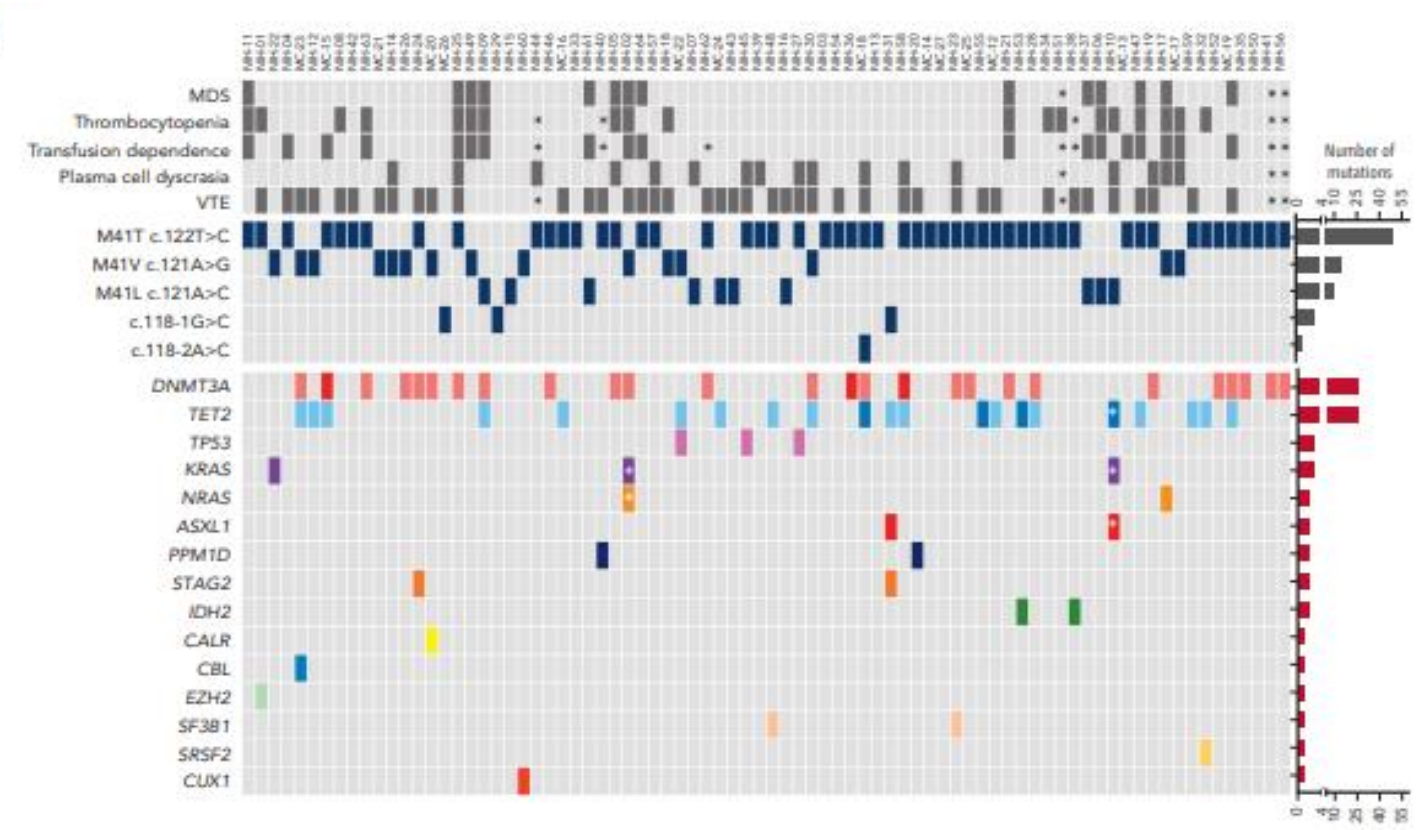


Beck D et al, N Engl J Med 2020;383:2628-38.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

UBA1 ed emopoiesi clonale

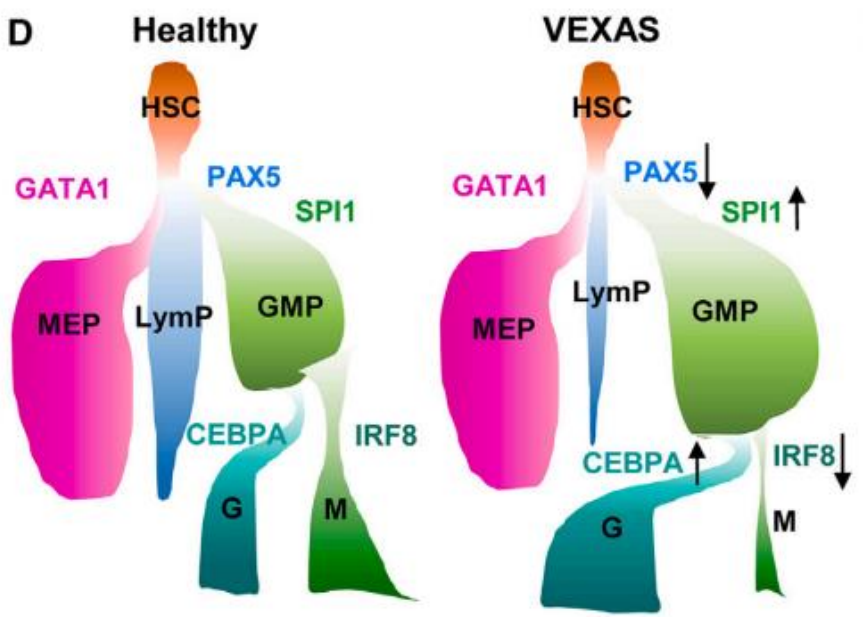


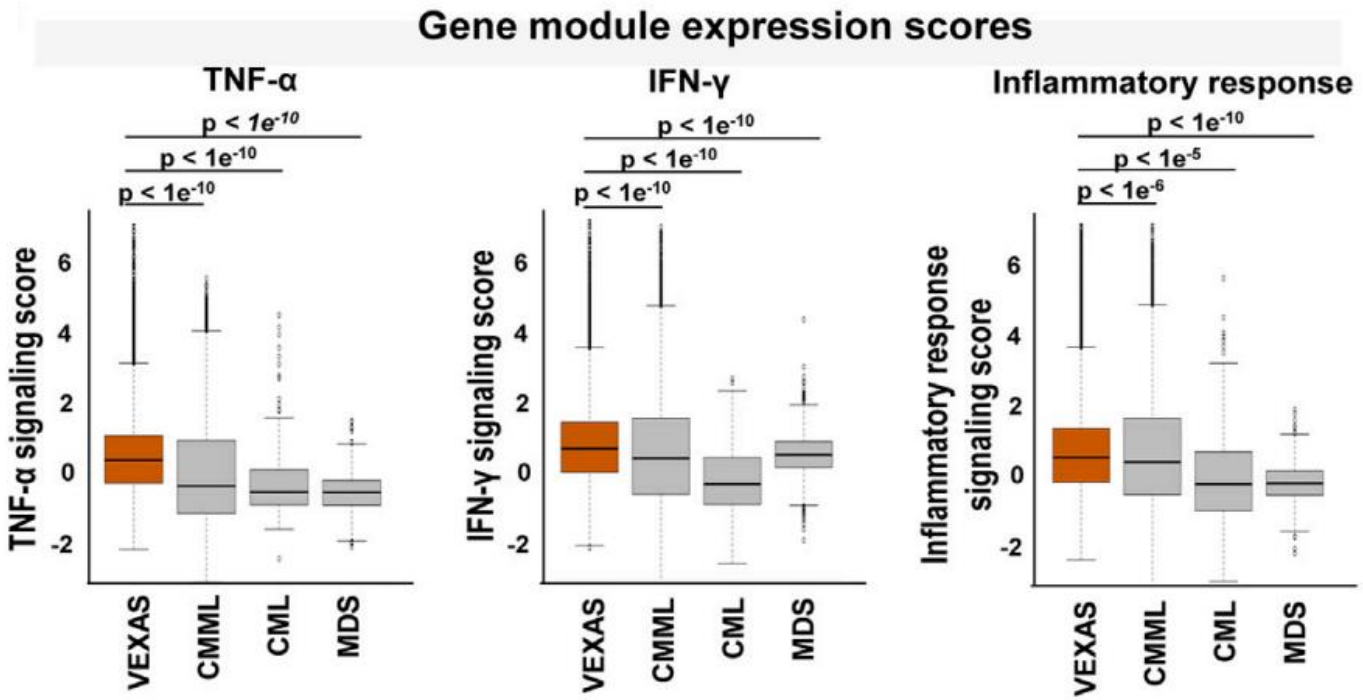


Blood (2023) 142 (3): 244–259.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Emopoiesi clonale con fenotipo autoinfiammatorio

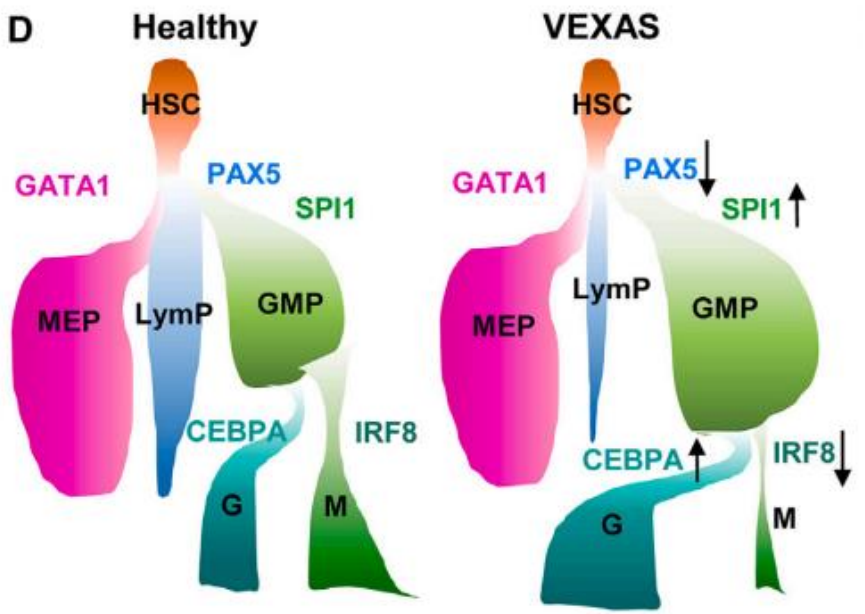


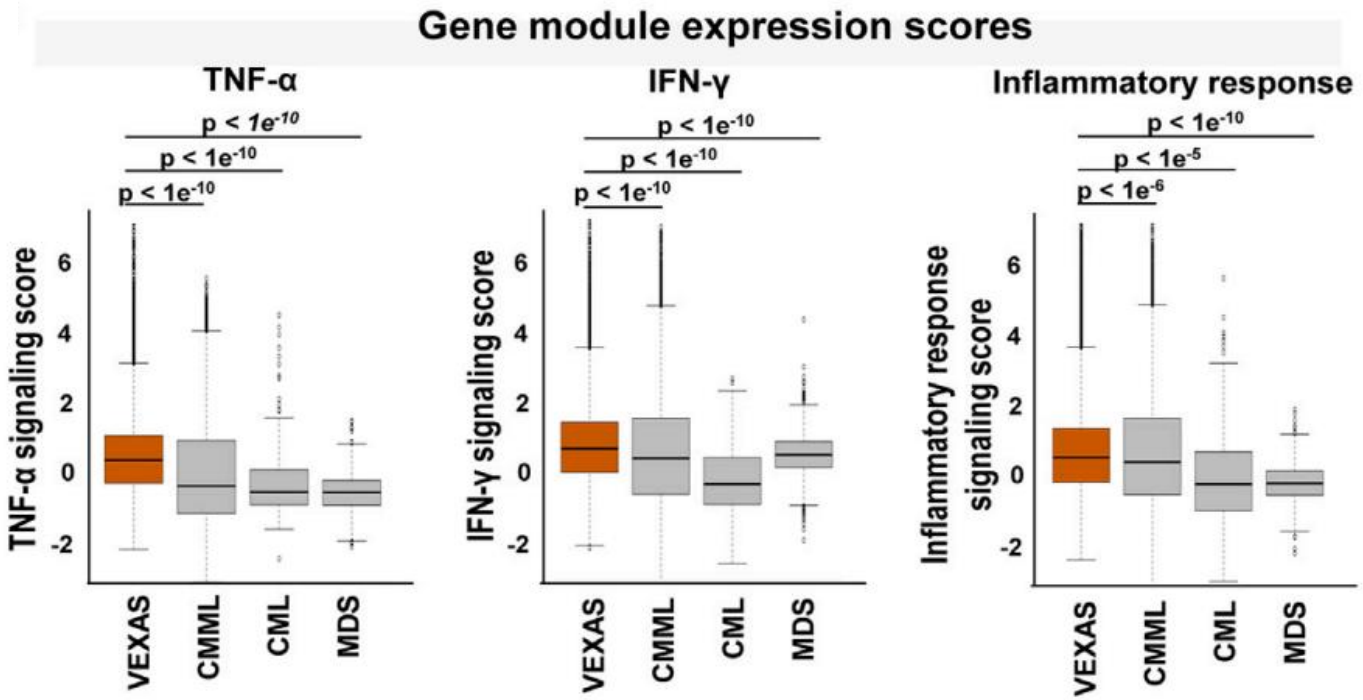


Cell Rep Med. 2023 Aug 15;4(8):101160.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Emopoiesi clonale con fenotipo autoinfiammatorio





- Anti IL1 (anakinra)
- Anti IL6 (tocilizumab)
- Anti JAK2 (ruxolitinib, baricitinib)

Cell Rep Med. 2023 Aug 15;4(8):101160.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome

Multi-omic approach confirmed that:

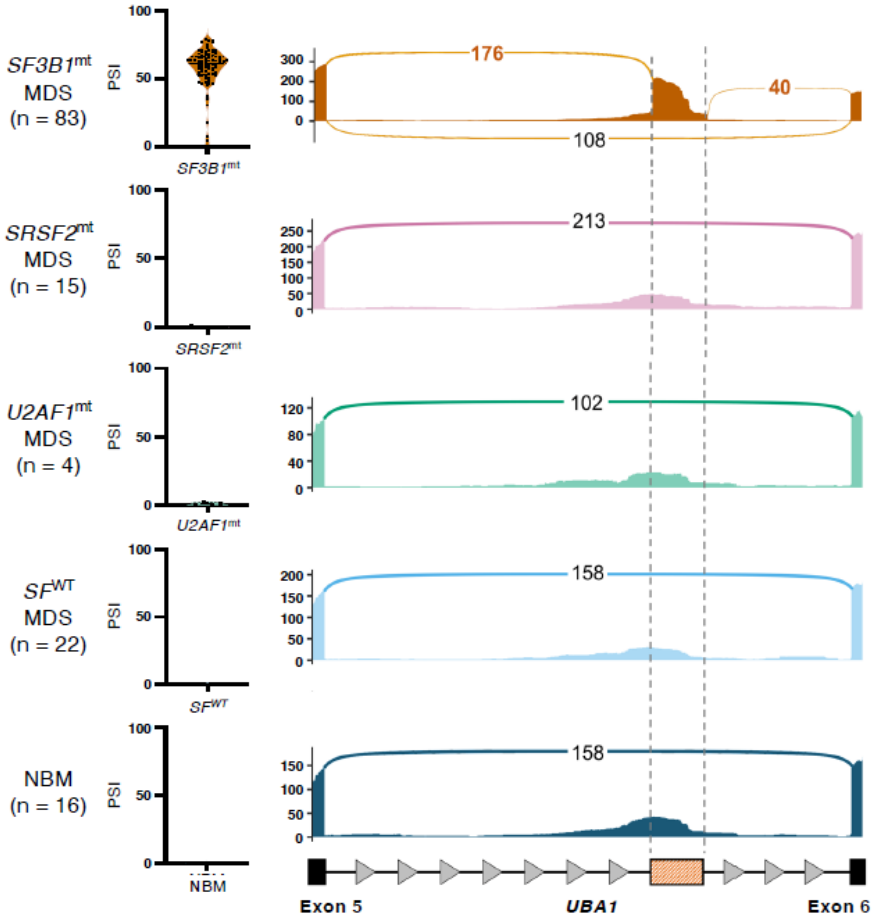
UBA1 somatic mutation drives clonal hematopoiesis

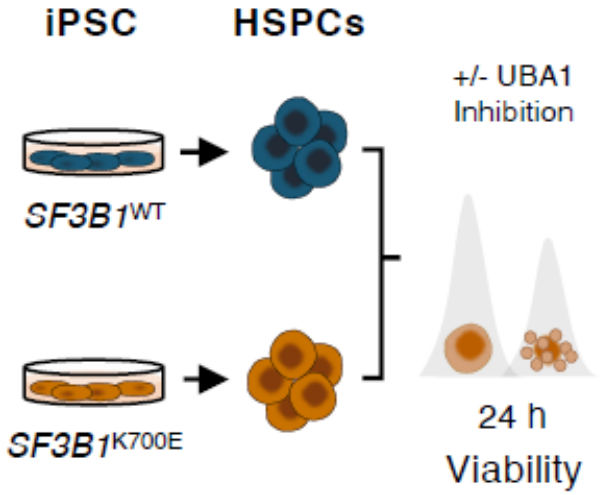
Inflammatory sympthoms are sustained by proinflammatory myeloid cells

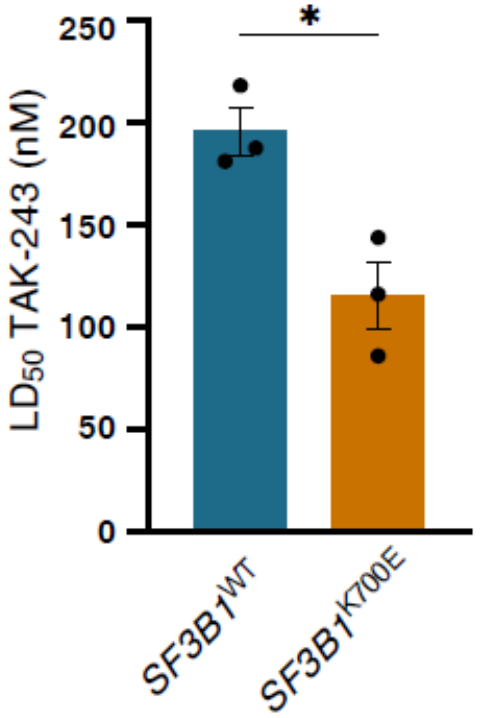
JAK/STAT, TNFa and IL1 pathways are promising therapeutic target

Cell Rep Med. 2023 Aug 15;4(8):101160.

MDS^{SF3B1mut} and VEXAS → closer than we thought







Jonas Thier et al, under review
(available on BioRxiv as 10.1101/2024.08.28.610114)

Take home message

1. Large multi-omic studies can overcome limitation of single NGS based knowledge

Take home message

1. Large multi-omic studies can overcome limitation of single NGS based knowledge

2. Multi-omic studies are very expensive, require strong biostatistics background and are usually driven by academic independent research (no company driven)

Take home message

1. Large multi-omic studies can **overcome** limitation of single NGS based knowledge

2. Multi-omic studies are very expensive, require strong biostatistics background and are usually driven by academic **independent** research (no company driven)

3. Validated results can prompt new diagnostic/prognostic assays development to inform clinicians on prognosis and response to treatment, promoting a **molecular-based** (rather than on average-based) **therapeutic decision making**.

Acknowledgment

IRCCS HUMANITAS RESEARCH HOSPITAL

C.A.L.R. CENTER FOR ACCELERATING LEUKEMIA/LYMPHOMA RESEARCH

Karolinska Institutet

GEN MED 4ALL

Horizon 2020
European Union Funding
for Research & Innovation

SYNTHEMA

FISiM FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

i nostri pazienti
(e i loro parenti)