CLONAL HEMATOPOIESIS IN GERMLINE PREDISPOSITION BACKGROUND: PREVALENCE AND DYNAMICS

Sandra Novoa-Jáuregui, Sara Torres-Esquius, Maria Gabarrós-Subirà, Francisco Beas, Ana María Garrido-Gómez, Claudia Pellín, Pamela Acha, Silvia Saumell, Ana Pérez, Adoración Blanco, David Valcárcel, Francesc Bosch, Andrés Jerez, Maria Julia Montoro

1. Servei d'Hematologia, Vall d'Hebron Universitari Hospital (VHUH), Barcelona
2. Vall 'Hebron Institute of Oncology, Barcelona

INTRODUCTION

Approximately **10% of adults** diagnosed with myelodysplastic neoplasms (MDS) or acute myeloid leukemia (AML) harbor **germline variants** in genes associated with predisposition to myeloid neoplasms. **Clonal hematopoiesis** (CH) has emerged as an area of interest in the context of germline predisposition (GP) in adults. However, the lack of longitudinal studies limits our understanding of CH as either a **pre-malignant condition** or a **compensatory mechanism** in a background of GP.

AIM

This study aimed to investigate the prevalence, evolution, and clinical implications of CH in relatives of adult patients with hematologic neoplasms of germline predisposition (HNGP) carrying familial pathogenic germline variants.

METHODS

GP SUSPECTED

GP-focused virtual exome-based panel on DNA extracted from hair-follicles and/or Telomere length (TL) measurement by flow-FISH

→ Index cases: **affected carriers**

Family cascade
Study by Sanger in PB or flow-FISH

Healthy carriers → Non-carriers (controls)

Somatic myeloid NGS panel +/- Telomere-mainteinance genes NGS panel — At baseline and 2- to 3 year follow-up

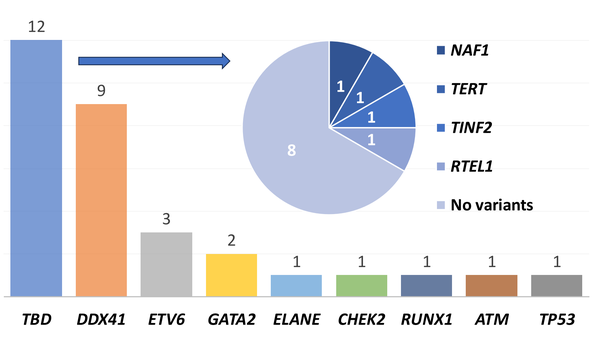
CH → **Risk stratification** according to Weeks et al. scoring system

Weeks et al. NEJM Evid 2023

RESULTS

Among the 201 patients with suspected GP, germline variants were identified in 30 index cases (Figure 1), median age at diagnosis 47 years (IQR 40-55).

Figure 1. Germline variants/TBD in index cases



Out of the 30 index cases, 133 family members were studied.

50 healthy carriers
median age 50 years, IQR 38.5-68.5

83 non-carriers
median age 57 years, IQR 39.5-67.5

41 (82%) underwent somatic NGS analysis

37 (44%) underwent somatic NGS analysis

12 (24%) harbored P/LP variants (Table 1)
median age at CH detection 62 years, IQR 47.5-76.5

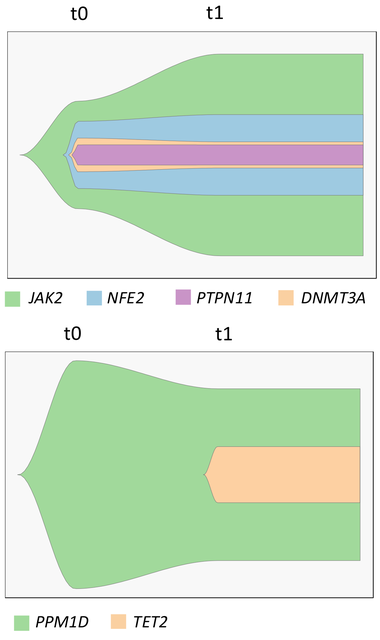
5 (13%) harbored P/LP variants
median age at CH detection 63 years, IQR 54-80.5

8 carriers re-evaluated after 2- to 3 year follow-up: 5 (62%) showed clonal evolution, either through an increase in VAF or the acquisition of new mutations. (Figure 2)

Table 1. CH in healthy carriers at baseline study and after 2- to 3 year follow-up period

INDEX CASE			HEALTHY CARRIERS			
			BASELINE NGS		FOLLOW-UP NGS	
DIAGNOSIS	GERMLINE VARIANT /TBD	Age at baseline study	SOMATIC VARIANT	VAF	SOMATIC VARIANT	VAF
MDS-RS	**TBD**	57	*PPM1D*	4.8%	*PPM1D* *TET2*	4.6% 1.5%
	TBD	45	*U2AF1*	4.7%	*U2AF1*	12%
DMS-MD	**TBD**	55	*DNMT3A*	1.7%	*TET2* *ASXL1*	1.3% 1%
Hypoplastic MDS	**TBD**	66	*PPM1D*	16.7%	No follow-up	
MDS-MD	***ETV6***	71	*TP53* *SRSF2*	4% 1.5%	*TP53*	4.3%
	ETV6	76	*DNMT3A* *JAK2* *NFE2* *PTPN11*	3.2% 16% 10% 5%	*DNMT3A* *JAK2* *NFE2* *PTPN11*	3% 30% 12% 2.2%
	ETV6	48	*CBL*	2.35%	No follow-up	
	ETV6	39	No variants		*KRAS*	1.3%
MDS-MD	***ETV6***	19	*KMT2A*	46%	No follow-up	
	DDX41	79	*DNMT3A*	3.1%	No follow-up	
AML	***DDX41***	81	*DNMT3A*	11,2%	No follow-up	
	DDX41	77	*DNMT3A*	2.8%	No follow-up	

Figure 2. Fish-plot showing clonal evolution in two different healthy carriers



Based on Weeks' risk score, 55% of CH in family carriers was classified as intermediate- or high-risk. Among non-carrier relatives, somatic variants were detected in 13.5% (median age 63 years, IQR 54-80.5), restricted to *DNMT3A* and *TET2,* all of them classified as low-risk CH. The difference in CH risk-score showed a trend toward statistical significance (p = 0.05).

CONCLUSIONS

We observed a high-risk profile CH among family carriers compared to non-carriers, most cases showing evidence of clonal evolution over time. Further studies will be needed to recommend CH surveillance to predict evolution to HN.

CONTACT

sandranovoa
@vhio.net