ÁREA: GENÉTICA Y GENÓMICA

Evaluación de la Hemopoyesis Clonal de potencial indeterminado (CHIP) en COVID-19

GRUPO DE
GENÉTICA Y GENÓMICA DE LOS TRASTORNOS DEL NEURODESARROLLO
Grupo de Genética y Genómica de Enfermedades Raras y Complejas

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ORIGINAL ARTICLE

Age-dependent association of clonal hematopoiesis with COVID-19 mortality in patients over 60 years

Marta Del Pozo-Valero · Marta Corton · Rosario López-Rodríguez · Ignacio Mahillo-Fernández · Javier Ruiz-Hornillos · Pablo Minguez · Cristina Villaverde · María Elena Pérez-Tomás · María Barreda-Sánchez · Esther Mancebo · the STOP_Coronavirus Study Group · Estela Paz-Artal Encarna Guillén-Navarro · Berta Almoguera · Carmen Ayuso

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2014 The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S.,

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,

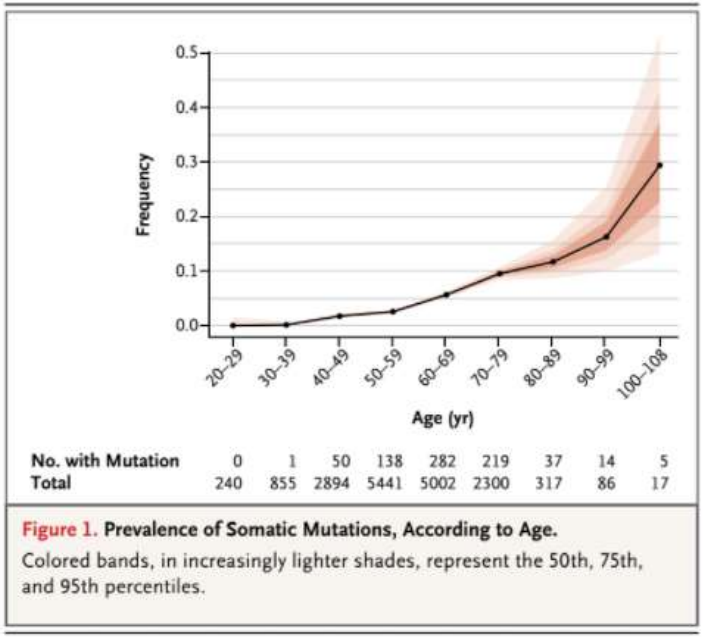
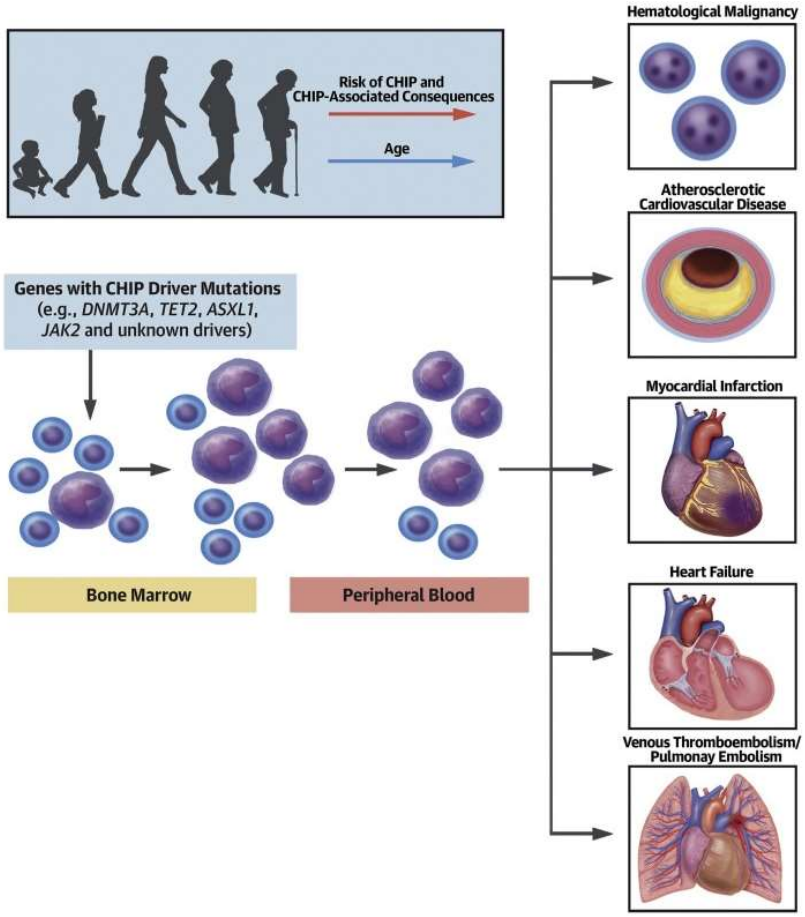


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

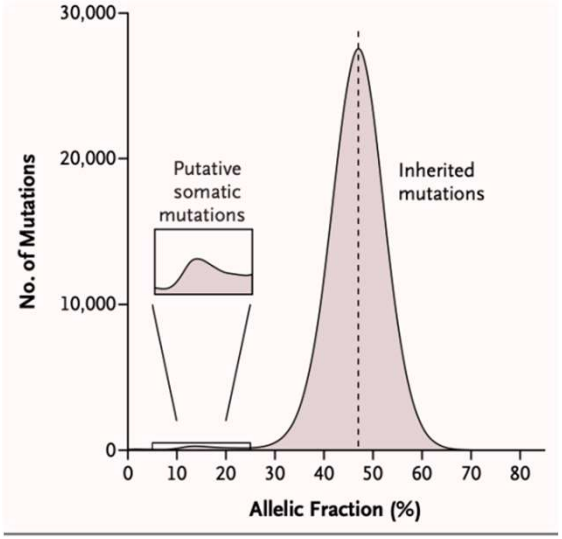
Age-related clonal hematopoiesis is a common condition that is associated with increases in the risk of hematologic cancer and in all-cause mortality, with the latter possibly due to an increased risk of cardiovascular disease.



Khetarpal, S.A. et al. J Am Coll Cardiol. 2019;74(4):578-86.

Clonal hematopoiesis (CH) refers to the expansion of hematopoietic cells with the same acquired mutation and is a common age-associated phenomenon in the general population

Clonal hematopoiesis of indeterminate potential (CHIP) denotes somatic mutations present with a variant allele fraction of >2% in genes involved in myeloid neoplasia in patients without overt hematological malignancy



CHIP-exacerbated inflammatory signaling may be associated with the severity of SARS-CoV-2 infection

ARTICLE
https://doi.org/10.1038/s41467-021-26138-6 OPEN
nature COMMUNICATIONS

Clonal hematopoiesis is associated with risk of severe Covid-19

Bolton et al., 2021

HemaSphere
Powered by EHA
EHA
Letter
OPEN ACCESS

Clonal Hematopoiesis in Hospitalized Elderly Patients With COVID-19

Hameister et al., 2020

Article

Clinico-Biological Features and Clonal Hematopoiesis in Patients with Severe COVID-19

Duployez et al., 2020

cancers

American Journal of Hematology

Petzer et al., 2021

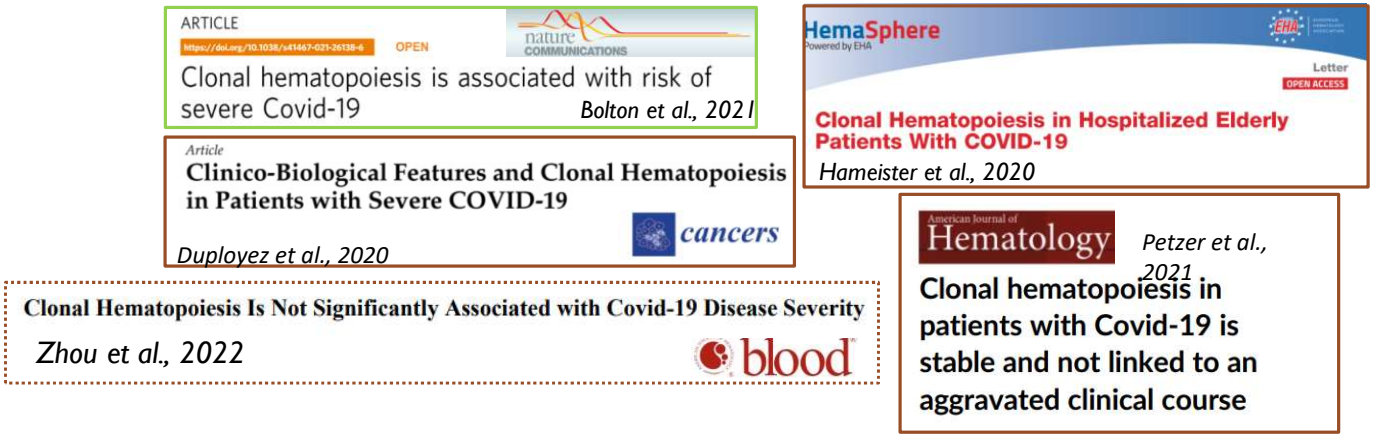
Clonal hematopoiesis in patients with Covid-19 is stable and not linked to an aggravated clinical course

Clonal Hematopoiesis Is Not Significantly Associated with Covid-19 Disease Severity

Zhou et al., 2022

blood

CHIP-exacerbated inflammatory signaling may be associated with the severity of SARS-CoV-2 infection



In this study, we aimed to determine if the presence of **CHIP was associated with COVID-19 mortality**, as the most severe outcome of the disease, in a cohort of 480 patients over 60 years infected with SARS-CoV-2.

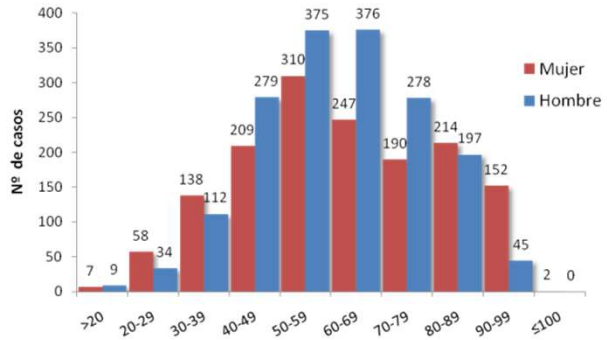
STOP_Coronavirus Study Group

Fondo COVID19-ISCIII COV20/00181:
STOP-Coronavirus: factores clínicos, inmunológicos, genómicos, virológicos y bioéticos de COVID-19
WP 3. Genómica del huésped.

3.872 pacientes de 4 hospitales:
-HU-FJD
-HU-IE
-HU-12O
-HU-VAM

Datos demográficos y clínicos:
-Leves/asintomáticos
-Hospitalizados
-Moderados
-Críticos/exitus

Datos genéticos:
Genotipado (GWAS)
Secuenciación masiva (WES, WGS, panel)




scientific reports

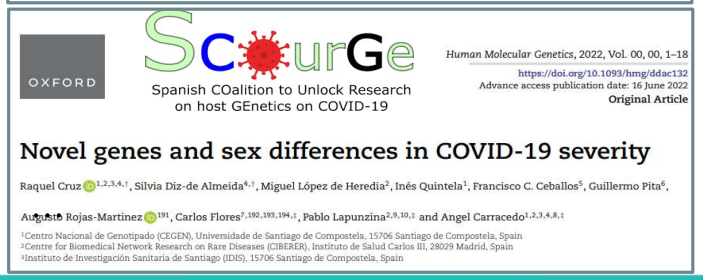
Presence of rare potential pathogenic variants in subjects under 65 years old with very severe or fatal COVID-19


ACCESS MICROBIOLOGY

SHORT COMMUNICATION

Soria et al., Access Microbiology 2021;3:000259
DOI 10.1099/acmi.0.000259

High SARS-CoV-2 viral load is associated with a worse clinical outcome of COVID-19 disease


OXFORD

SCurGe
Spanish COalition to Unlock Research on host GEnetics on COVID-19

Human Molecular Genetics, 2022, Vol. 00, 00, 1–18
https://doi.org/10.1093/hmg/ddac132
Advance access publication date: 16 June 2022
Original Article

Novel genes and sex differences in COVID-19 severity

STOP_Coronavirus Study Group

>60 years
Matched by age and sex
No history of hematological cancer

DECEASED
N=241

SURVIVORS
N=239

Myeloid Solutions™ Panel (SOPHiA Genetics)
30 genes implicated in hematological malignancies
Mean coverage: 4131X
>99% of the target regions with coverage ≥1000X

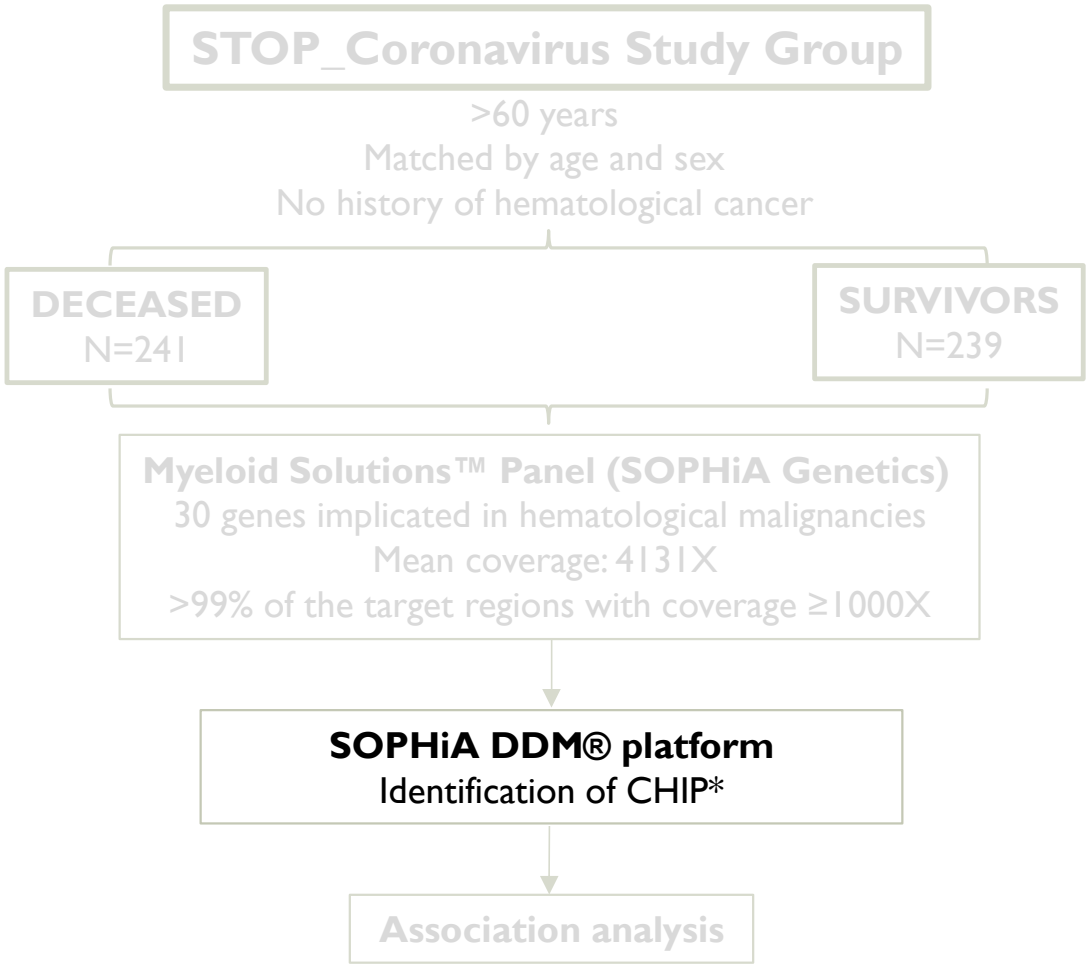
↓

SOPHiA DDM® platform
Identification of CHIP*

↓

Association analysis

ABL1	*FLT3*	*PTPN11*
ASXL1	*HRAS*	*RUNX1*
BRAF	*IDH1*	*SETBP1*
CALR	*IDH2*	*SF3B1*
CBL	*JAK2*	*SRSF2*
CEBPA	*KIT*	*TET2*
CSF3R	*KRAS*	*TP53*
DNMT3A	*MPL*	*U2AF1*
ETV6	*NPM1*	*WT1*
EZH2	*NRAS*	*ZRSR2*



Criteria for CHIP:

1) VAF between 2% and 35%
2) Missense, frameshift, stop-gain, in-frame indel, and splice canonical sites
3) MAF <1% in population databases
4) MAF <2% in our cohort of patients
5) Variant not benign or likely benign in ClinVar.

Classification was based on the Belgian next-generation sequencing guidelines for hematological and solid tumors

Categories: variants of unknown clinical significance (**VUS**); and likely pathogenic (**LP**) and pathogenic (**P**) variants.

Cohort characteristics

Variables	All patients	Deceased (N=241)	Survivors (239)	p-value
Age (mean±SD)	82.1±10.4	82.6±10.7	81.6±10.0	0.306
Male	54.2% (260/480)	51.9% (125/241)	56.5% (135/239)	0.310
Europeans	92.9% (446/480)	94.2% (227/241)	91.6% (219/239)	0.274
Comorbidities				
Obesity	25.3% (81/320)	25.5% (38/149)	25.2% (43/171)	0.942
Cardiovascular disease	25.1% (110/438)	27.4% (61/223)	22.8% (49/215)	0.271
Hypertension	68.2% (317/465)	65.7% (151/230)	70.6% (166/235)	0.248
Diabetes	16.9% (75/445)	17.0% (38/223)	16.7% (37/222)	0.916

Patients were stratified by age:
60-74 years (N=124; 48.4% deceased)
75-84 years (N=125; 41.6% deceased)
85-91 years (N=132; 56.8% deceased)
92-101 years (N=99; 54.5% deceased)

CHIP

38% patients carried CHIP: no difference between deceased and survivors

*CHIP in cohorts published: 10%-25%

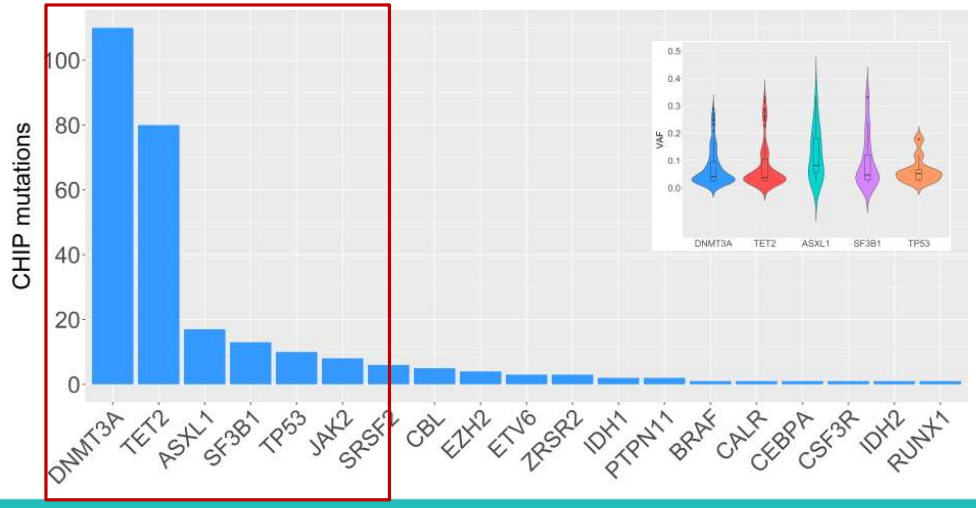
269 CHIP in 19 different genes

-61% P/LP

-39% VUS

85.5% of the variants identified were in 5 genes

51.7% (139/269) had a VAF <5%

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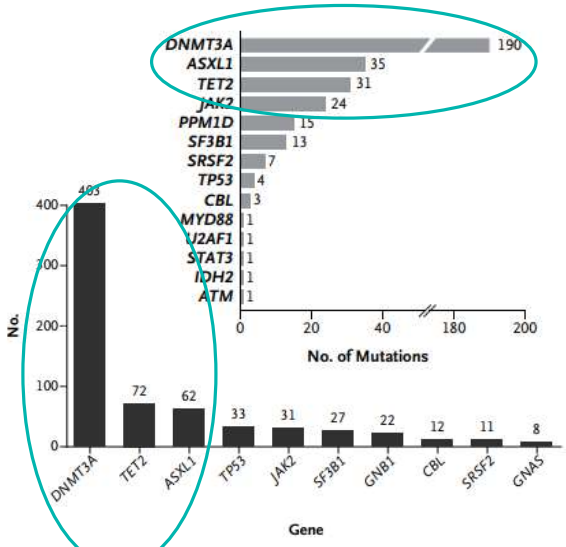
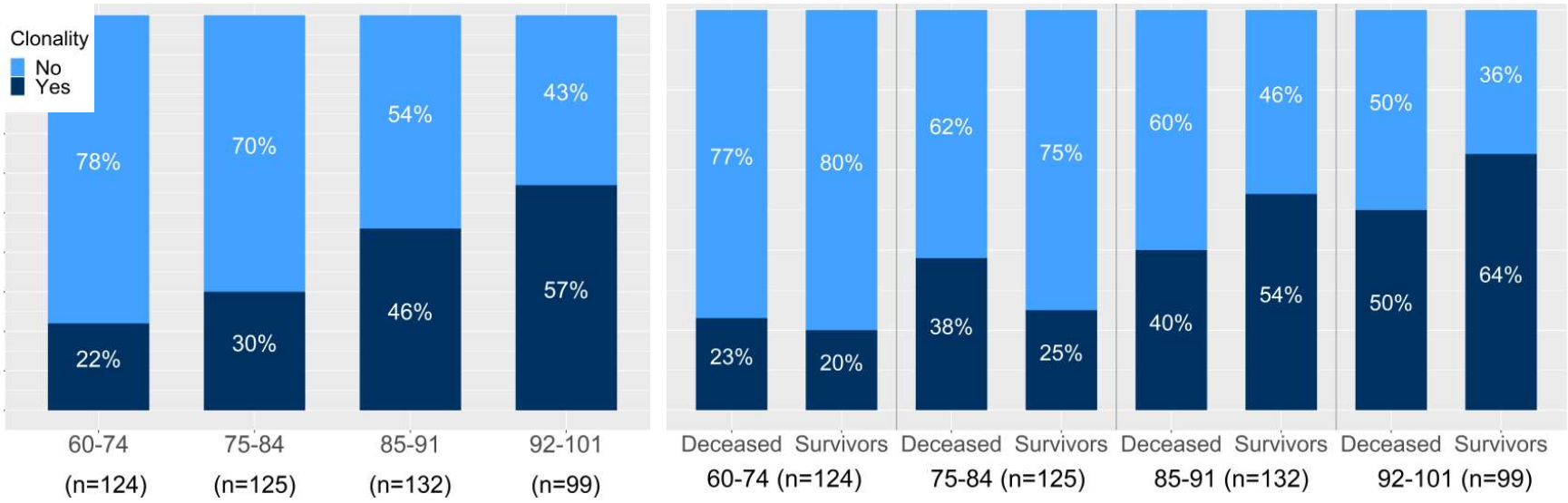


The presence of CHIP increased with age



Outcome	Predictor	Stratum	OR	(95% CI)	P-value
Clonality	Age	Total	1.05	(1.03, 1.08)	<0.001
		Deceased	1.03	(1.00, 1.06)	0.081
		Survivors	1.08	(1.04, 1.12)	<0.001
Mortality	Clonality	Total	0.98	(0.67, 1.43)	0.899
		60-74	1.21	(0.49, 3.00)	0.680
		75-84	1.66	(0.71, 3.87)	0.241
		85-91	0.58	(0.28, 1.19)	0.136
		92-101	0.66	(0.28, 1.58)	0.348
	Clonal variants	Total	0.97	(0.78, 1.20)	0.764
		60-74	1.02	(0.55, 1.89)	0.957
		75-84	1.78	(0.95, 3.35)	0.071
		85-91	0.75	(0.49, 1.17)	0.202
		92-101	0.74	(0.50, 1.08)	0.115
	P/LP variants	Total	0.93	(0.72, 1.19)	0.550
		60-74	0.72	(0.30, 1.69)	0.444
		75-84	2.72	(1.18, 6.29)	0.020
		85-91	0.70	(0.42, 1.14)	0.151
		92-101	0.64	(0.41, 1.01)	0.055
	VUS variants	Total	1.11	(0.70, 1.76)	0.650
		60-74	1.92	(0.61, 6.02)	0.261
		75-84	0.70	(0.21, 2.31)	0.554
		85-91	0.98	(0.43, 2.20)	0.958
		92-101	1.15	(0.43, 3.07)	0.772
	VAF	Total	1.03	(0.85, 1.26)	0.743
		60-74	1.14	(0.71, 1.83)	0.595
		75-84	1.30	(0.78, 2.16)	0.305
		85-91	0.93	(0.64, 1.35)	0.708
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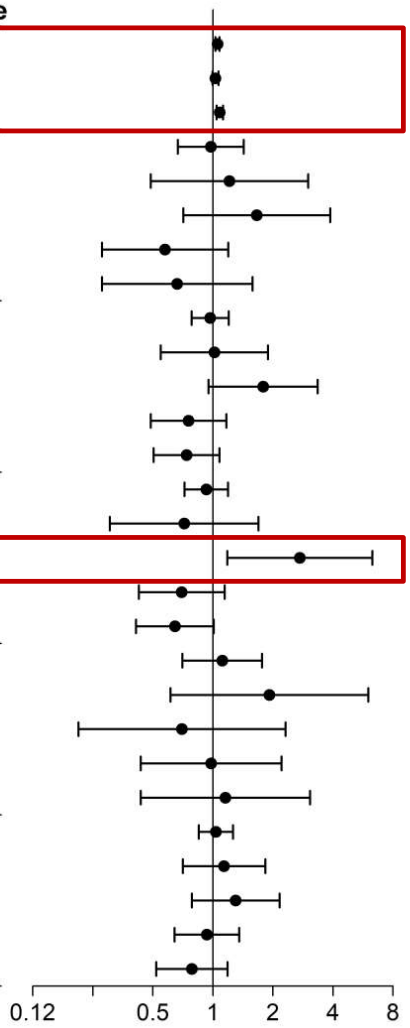

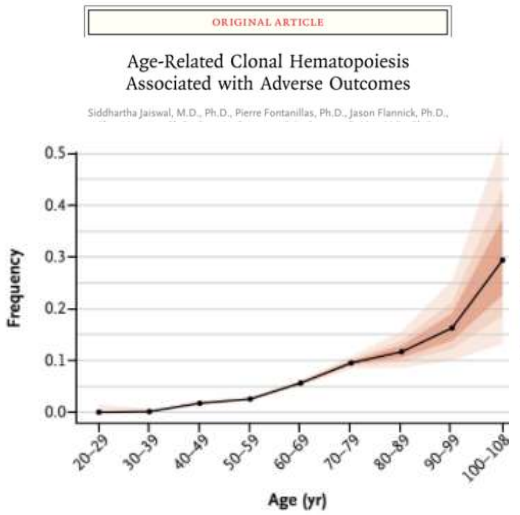

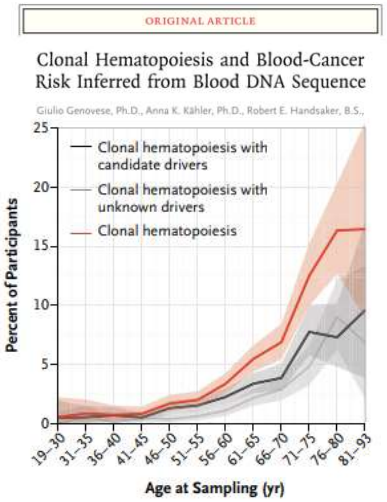

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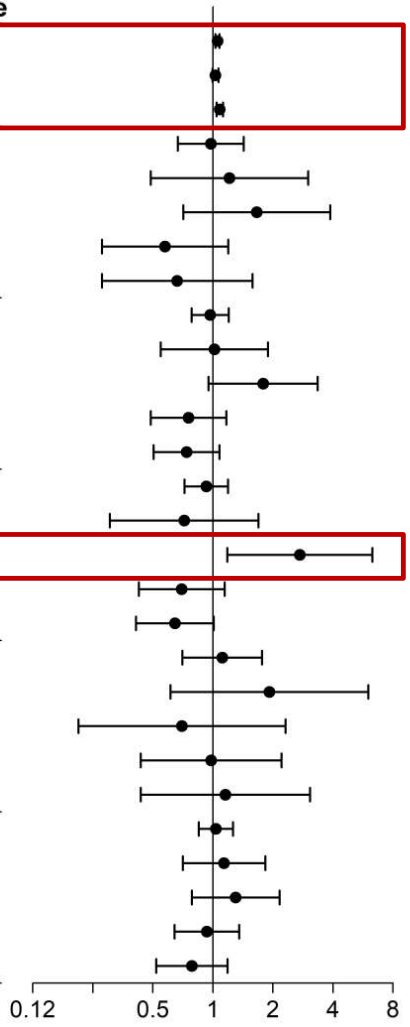

Gene-specific, age-dependent clonal expansion
Socio-sanitary factors
Spurious association

Conclusions

Confirm the well-established association of CHIP with age

Main genes: *DNMT3A*, *TET2*

LP/P variants in patients 75-84 years

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