Clonal hematopoiesis is associated with increased risk of progression of asymptomatic Waldenström Macroglobulinemia

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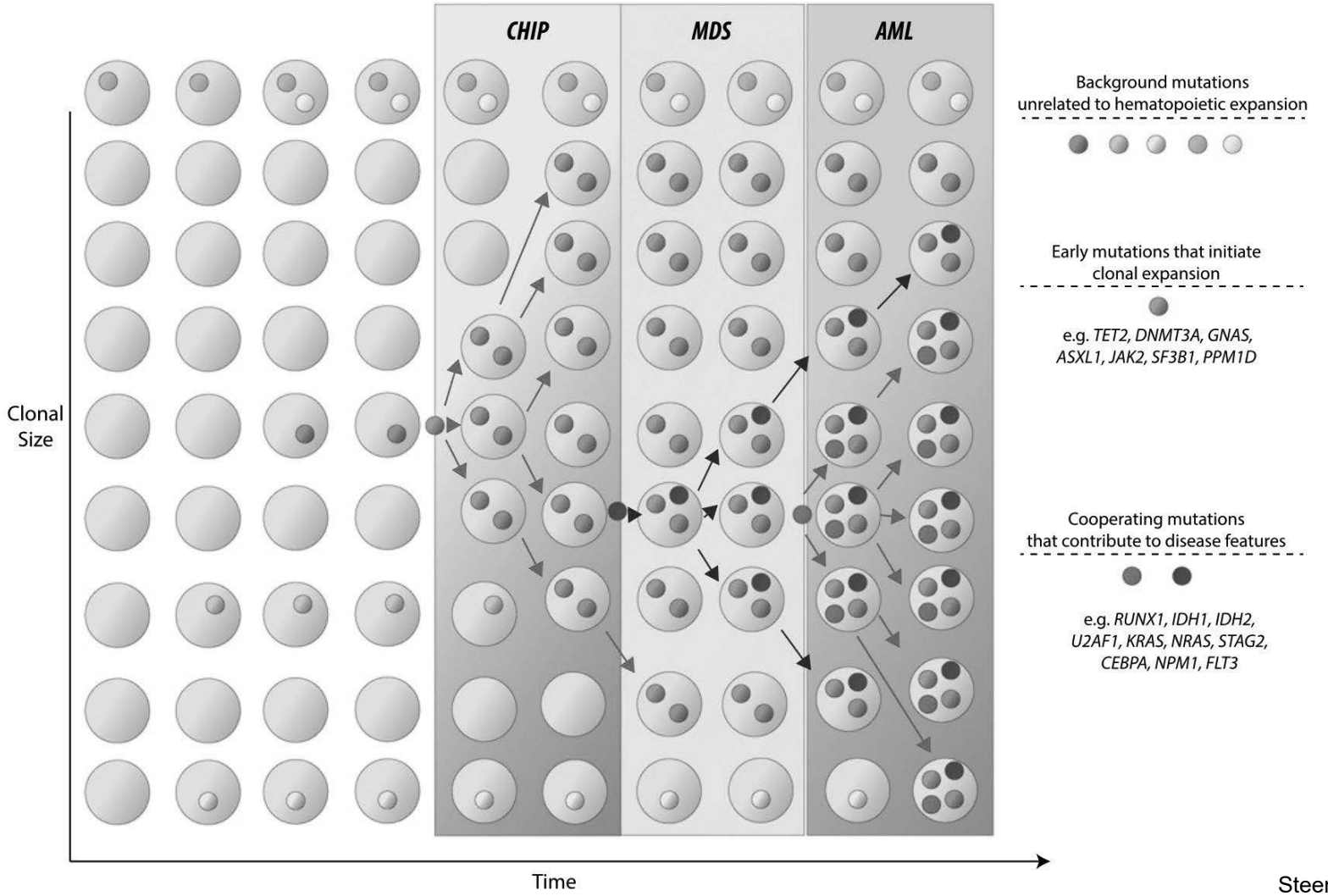
Disclosure Information

- I have no financial relationships to disclose.

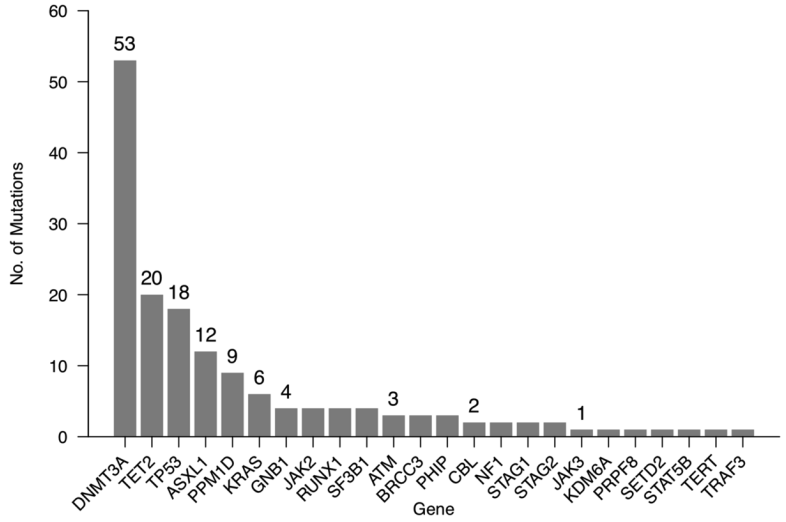
Clonal Hematopoiesis of Indeterminate Potential (CHIP)



Steensma DP, et al. Blood. 2015; 126: 9-16.

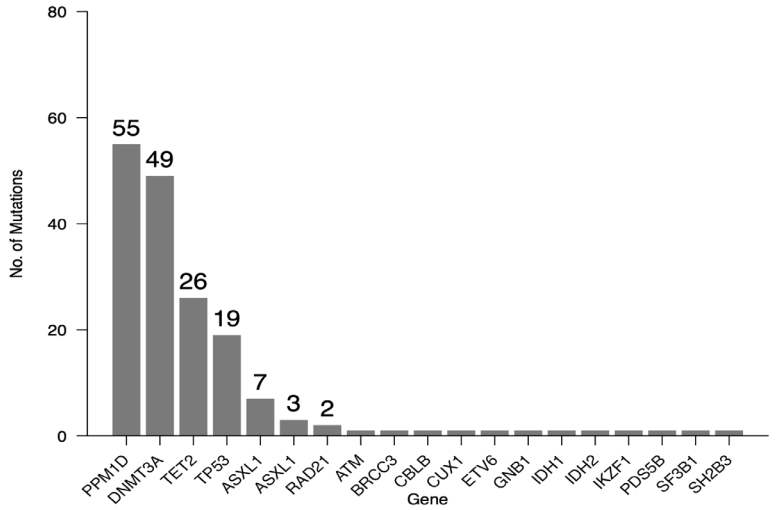
Clonal hematopoiesis (CH) and hematological malignancies

Multiple Myeloma (MM) at time of ASCT



Mouhieddine TH, et al. Nature Comm. 2020; 11 (1).

Non-Hodgkin lymphoma (NHL) at time of ASCT



Gibson CJ, et al. J Clin Oncol. 2017; 35: 1598-1605.

Waldenström Macroglobulinemia (WM)

Indolent NHL characterized by immunoglobulin-M (IgM) secreting lymphoplasmacytic cells and hallmark mutations in genes involved in B-cell signaling, including *MYD88* and *CXCR4*

Symptomatic patients are managed by cytotoxic chemotherapy, proteasome inhibitors, Bruton tyrosine kinase (BTK) inhibitors and anti-CD20 antibodies

Genomic profiling is of importance in treatment selection

Many patients present with precursor stages IgM MGUS and smoldering WM and do not require treament at time of diagnosis

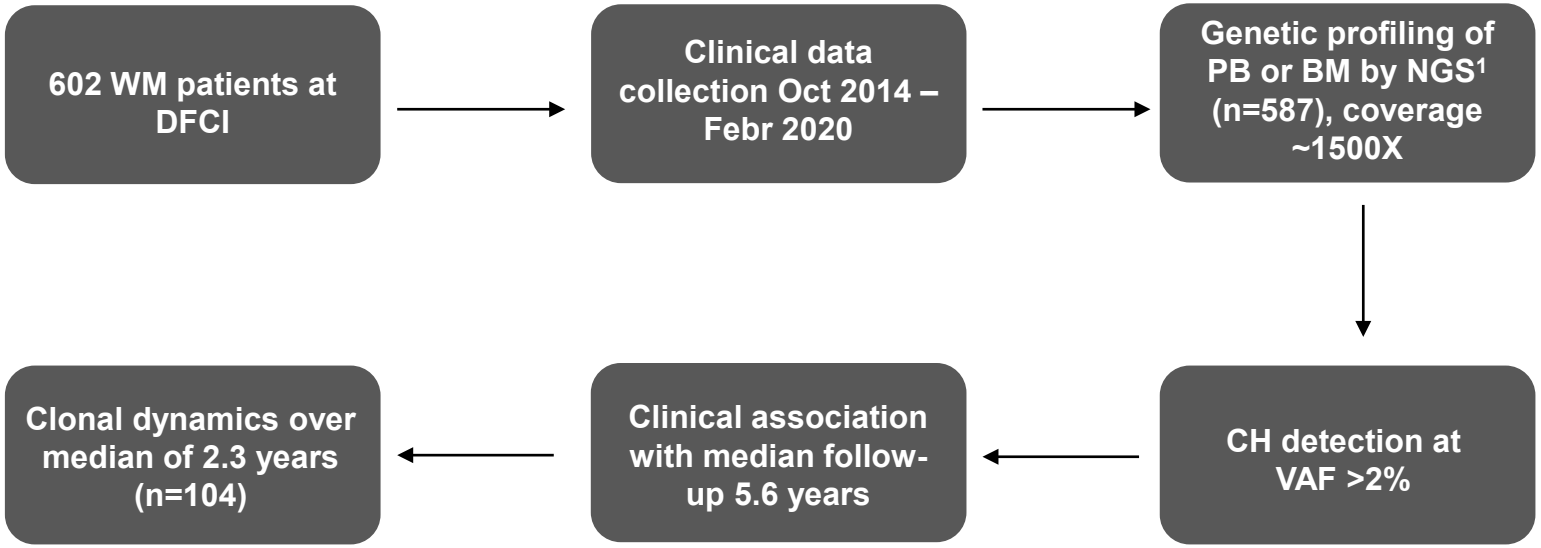
Dimopoulos MA, et al. Blood. 2019;134(23:2022-2035.
Treon SP, et al. Hematol Oncol Clin North Am. 2018:32(5):745-752.
Treon SP, et al. J Clin Oncol. 2020; 38(11):1198-1208
Branagan AR, et al. Leuk Lymphoma. 2021;62(8):1805-1815.
Bustoros et al. J Clin Oncol. 2019;37(16):1403-1411.

Study Aims and Objectives

1. To investigate the frequency of CH in Waldenström Macroglobulinemia

2. To study the association of CH mutations with clinical outcome in WM patients

Study Workflow



Thirteen patients (3%) had a coincident diagnosis of MDS or AML and one had ALL at the time of NGS; these 14 patients were excluded from further analysis

CH was defined by the presence of somatic mutations in *DNMT3A*, *TET2* or *ASXL1* (CH-DTA)

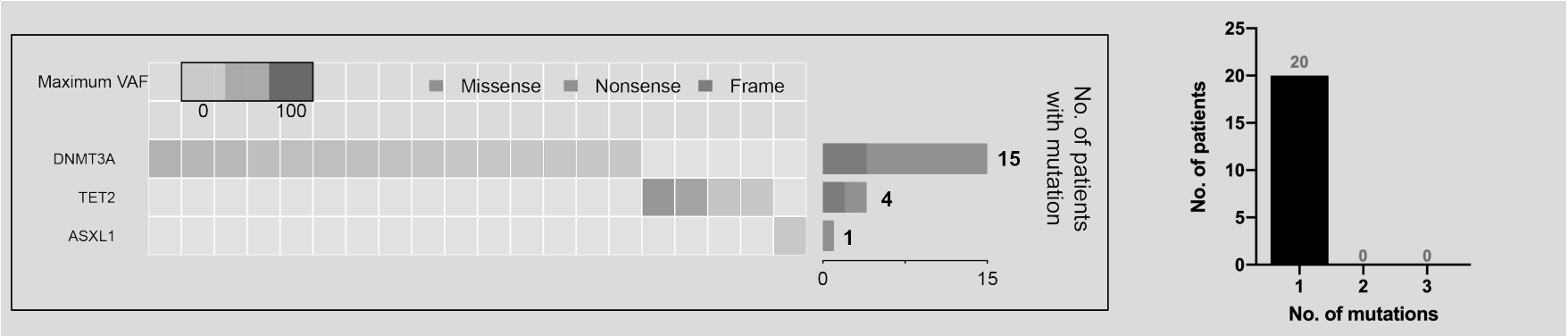
[1] Kluk et al. J Mol Diagn. 2016;18(4):507-515.

Study Cohort Baseline Characteristics (n=587)

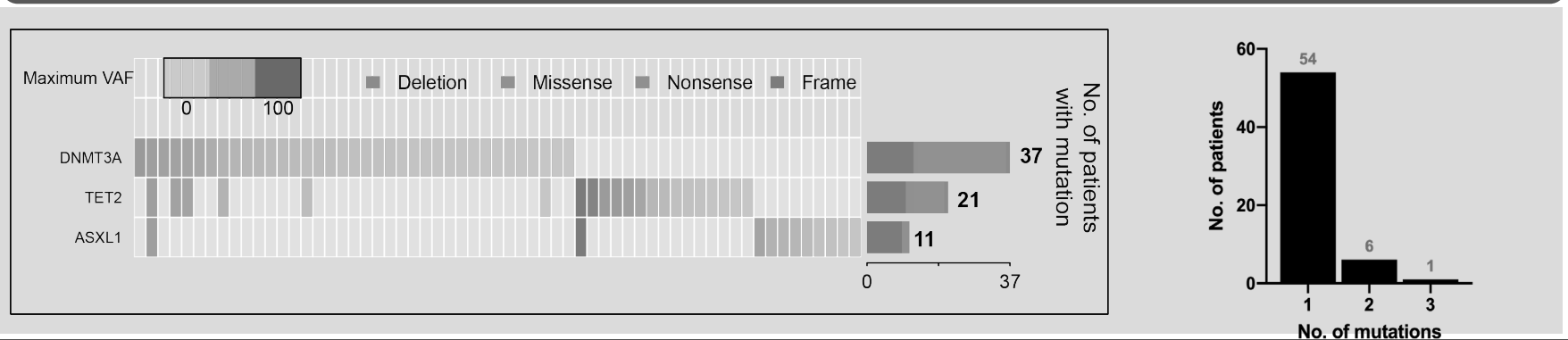
	Asymptomatic WM (n=147)	Symptomatic WM (n=440)
Age at NGS *Median (range)*	66 (40-89)	68 (33-93)
Sex *Female* *Male*	 69 (47%) 78 (53%)	 161 (37%) 279 (63%)
Diagnosis *MGUS* *SWM* *WM*	 31 (21%) 116 (79%) -	 - - 440 (100%)
BM involvement at NGS *Median (range)*	20 (0.3-95%)	50 (0-95)
Cytotoxic therapy pre-NGS	0 (0%)	141 (32%)
IgM at NGS *Median (range)*	1228 (134-7554)	1706 (15-8310)
MYD88 mutation (PCR)	113 (77%)	369 (84%)

CH-DTA is present in at least 14% of WM patients

Asymptomatic WM
CH frequency: IgM MGUS: 13%; SWM: 14%

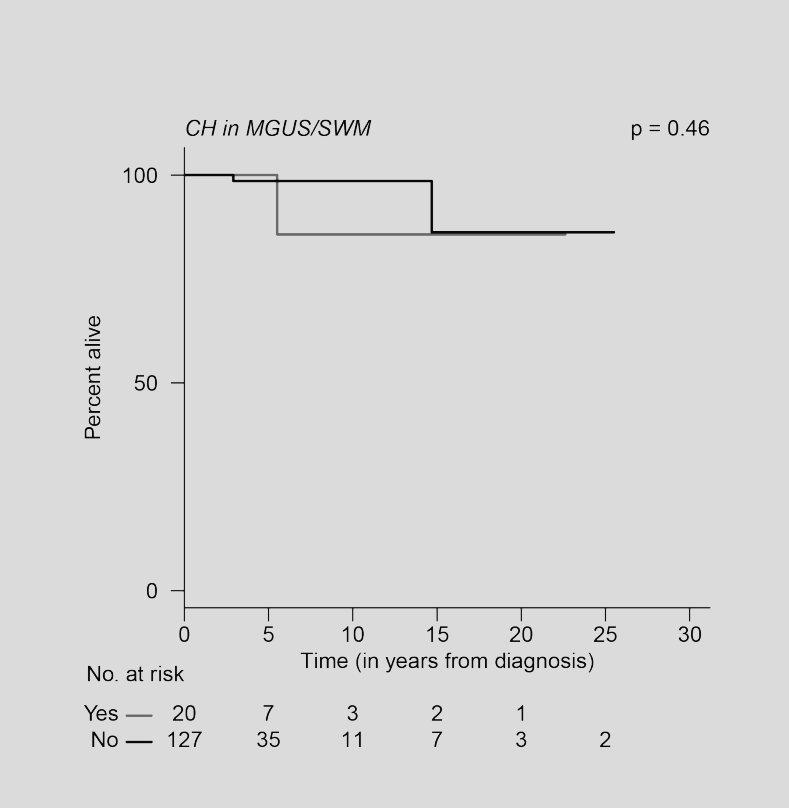


Symptomatic WM
CH frequency: 14%

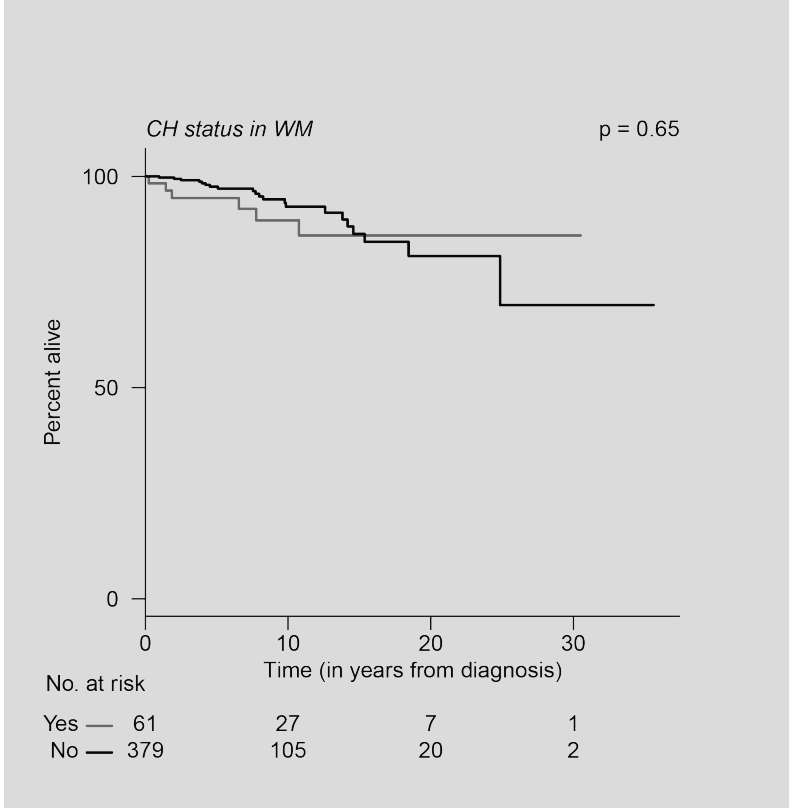


CH-DTA is not associated with inferior OS

Asymptomatic WM



Symptomatic WM



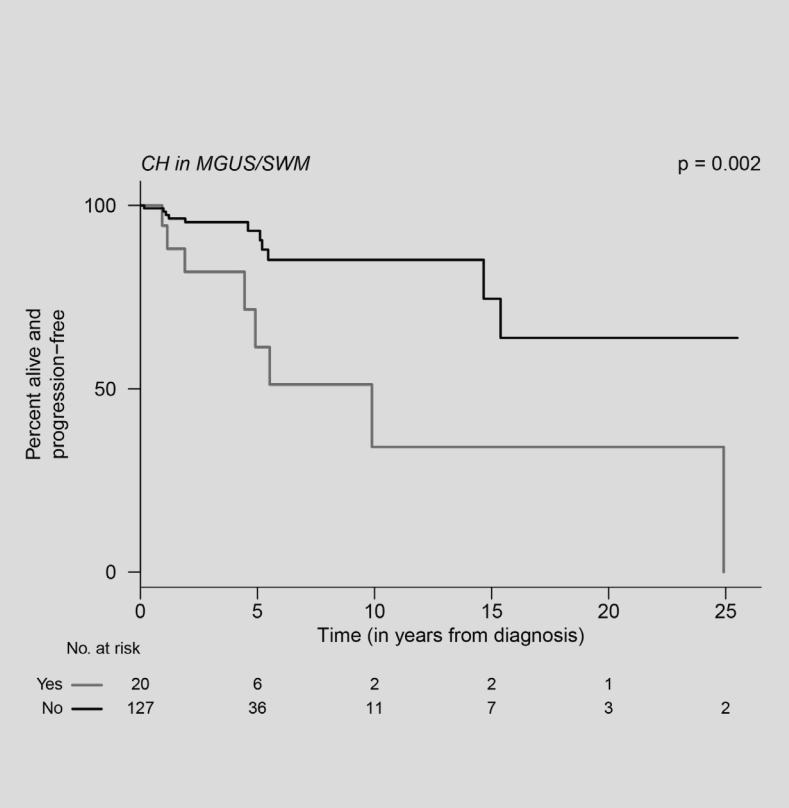
CH-DTA mutation

No CH-DTA mutation

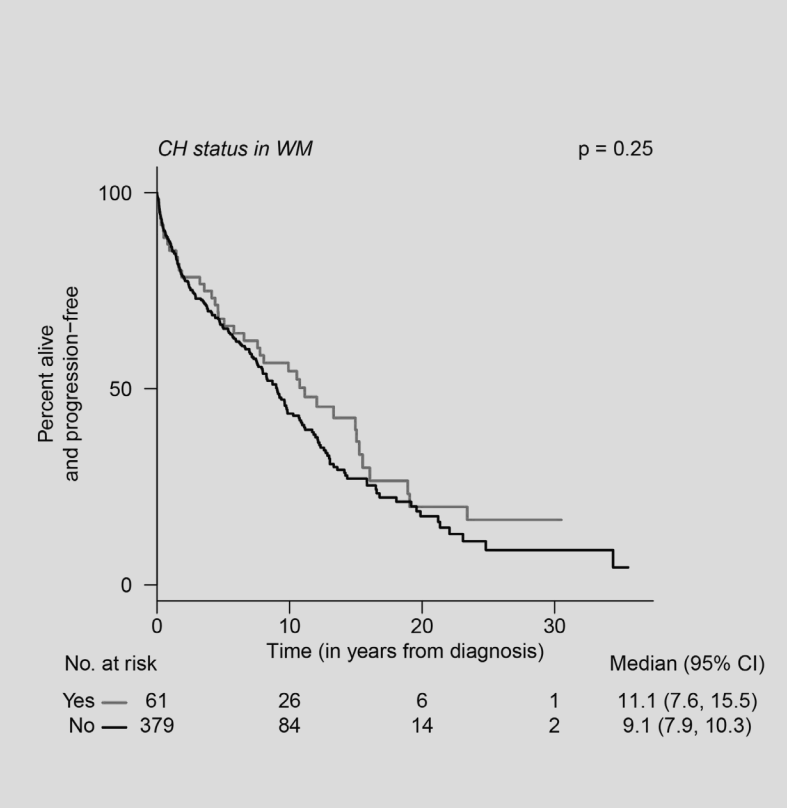
Median follow-up from diagnosis and NGS assay of 6.7 (95% CI: 6.1-7.6) and 2.5 (95% CI: 2.2-2.8) years

Asymptomatic WM patients with CH-DTA have an increased risk of progression

Asymptomatic WM



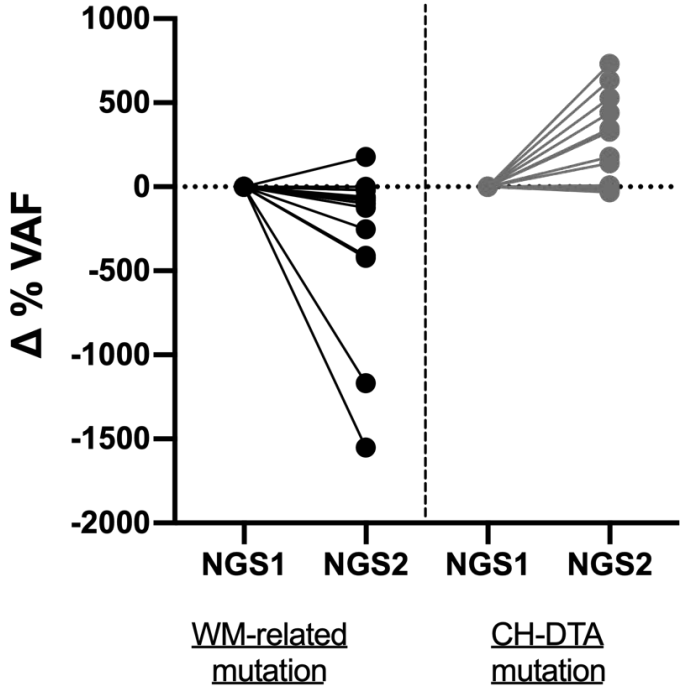
Symptomatic WM



CH-DTA mutation

No CH-DTA mutation

Clonal dynamics of WM-related mutations and CH-DTA mutations in response to therapy



Summary

CH is present in at least 14% of patients with WM.

Patients with CH are more likely to progress from IgM MGUS or smoldering WM to symptomatic WM.

No indication for changes in clinical management for WM patients with coexistent CH.

Further work is needed to determine how the presence of CH might promote progression to WM and whether it can be incorporated into risk stratification models.

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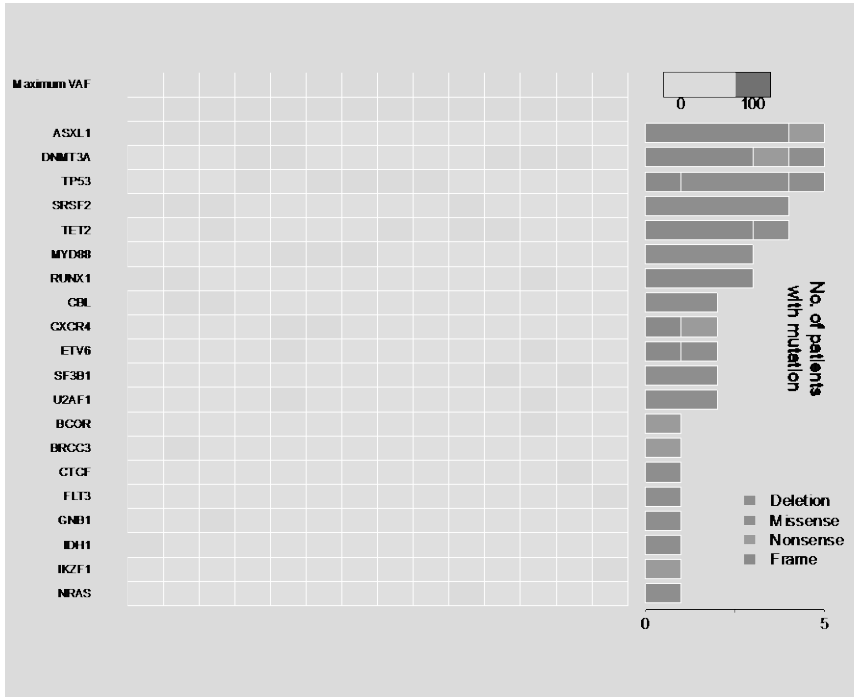
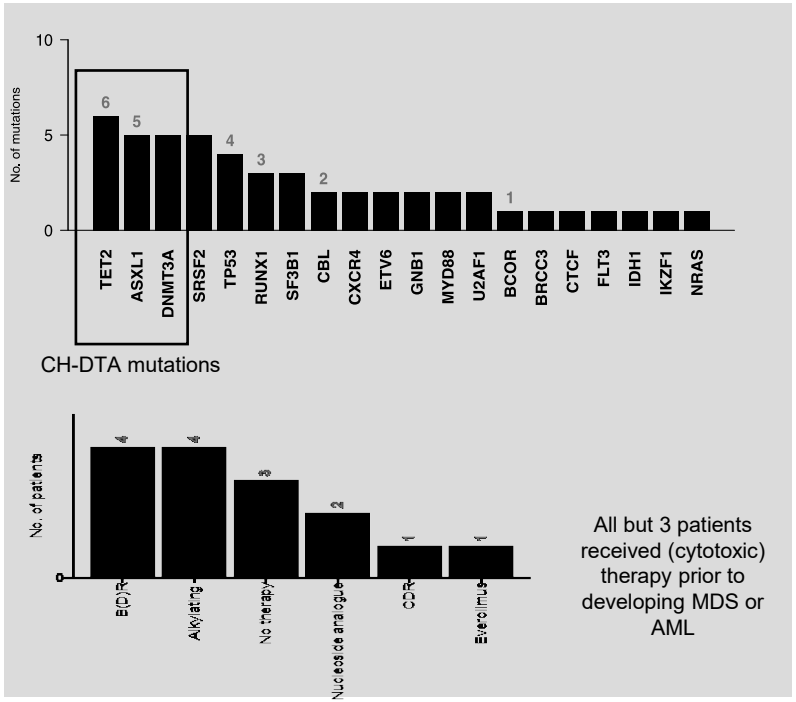
TMN risk

Increased risk of MDS and AML is well documented in WM and CH is associated with increased myeloid malignancy risk. We performed an exploratory analysis of patients with both WM and a myeloid malignancy.





Fourteen patients had a concurrent myeloid malignancy at the time of NGS, developing at a median of 7.9 years from WM diagnosis, 13 of which were MDS (87%). During follow-up, 1 additional patient with *SF3B1* and *SRSF2* mutations developed MDS after receiving bendamustine and rituximab.

Detection of mutated CXCR4 and MYD88 by diagnostic NGS in WM

Recent studies have shown CXCR4 and MYD88 detection is impaired by NGS in WM

- **Previous literature:** 90-95% *MYD88*; 40% *CXCR4*.
- Based upon studies using AS-PCR on CD19-selected BM to maximize sensitivity.

- **Our cohort** showed lower detection levels of *MYD88* and *CXCR4* by NGS, see below table:

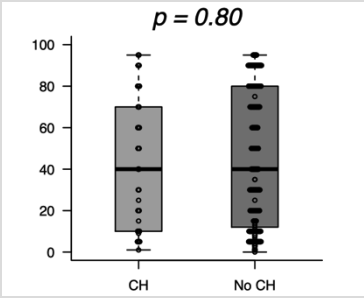
	Asymptomatic WM (n=147)	Symptomatic WM (n=440)
Mutation *MYD88*	51 (34.7%)	200 (45.5%)
Mutation *CXCR4*	14 (9.5%)	75 (17%)

- ***Gustine et al:*** 40% vs 15% when comparing AS-PCR on CD19 selected BM vs NGS on unselected BM (n=107, WM); 63% false-negatives.
- ***Kofides et al.:*** 66% of MYD88 mutations detected by AS-PCR on CD19-selected BM by NGS on unselected BM.

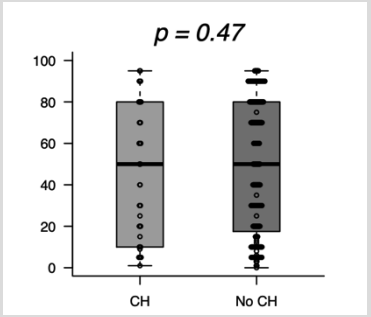
- Sensitivity of *CXCR4* and *MYD88* mutations was impacted by bone marrow involvement (patchy BM and/pr hemodilution).

- In our cohort no indication CH-DTA detection was influenced by BM involvement (biopsy or aspirate).

Asymptomatic WM



Symptomatic WM



Gustine et al. Br J Haematol. 2021;194(4):730-733.
Kofides et al. Hemasphere. 2021:5(8):e624.

Was the presence of MYD88 L265P (or absence) associated with CH-related mutations?