Spectrum, Prevalence, and Clinical Correlates of *PPM1D* Mutations in Patients with Clonal Haematopoiesis and Clonal Cytopenias

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BACKGROUND

TP53 and *PPM1D* are key regulators of DNA damage response and repair, and somatic mutations in these genes often co-occur in haematopoietic cells, expanding under genotoxic stress. Unlike with *TP53* mutations, where mechanisms of progression are defined,[1] the pathways underlying clonal fitness and transformation in mutant *PPM1D* remain poorly defined.[2,3]

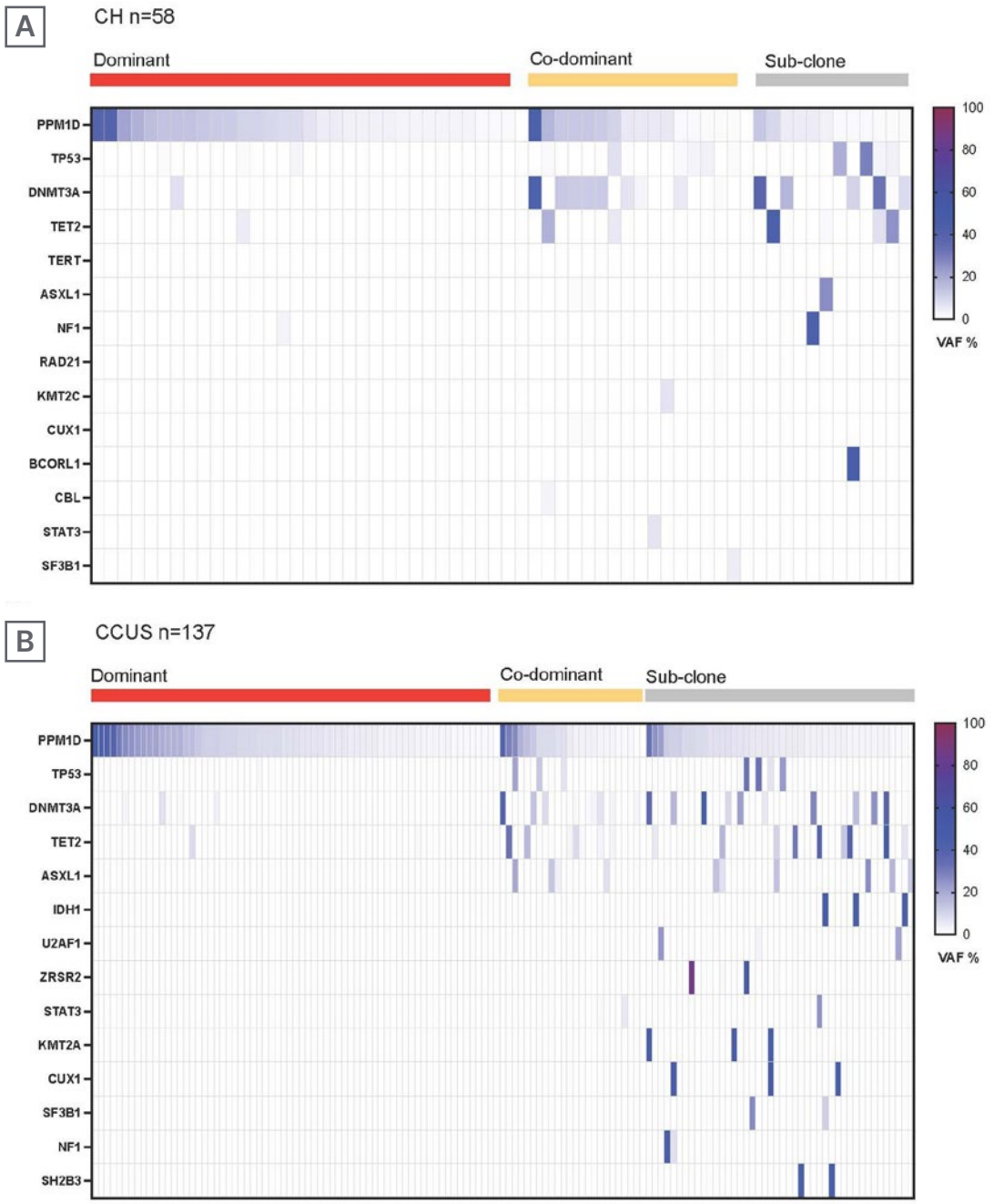
METHODS

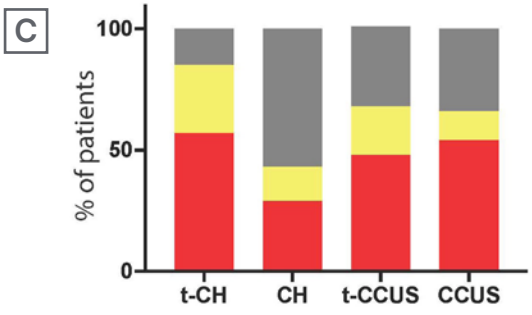
In collaboration with five academic institutions, the authors analysed the clinical and molecular landscape of 337 patients with clonal haematopoiesis (CH) and clonal cytopenia of undetermined significance (CCUS) across four genotypes: *PPM1D* mutations (mt)/*TP53*-wild type (wt) (n=170 [50%]), *PPM1D*mt/*TP53*mt (n=25 [7%]), *TP53*mt/*PPM1D*wt (n=17 [5%]), and *TP53*wt/*PPM1D*wt (n=125 [38%]).[4]

RESULTS

All *PPM1D* variants were truncating, located in exon 6 of the gene, with a median variant allele frequency (VAF) of 6% (0.3–64%). Patients with *PPM1D*mt/*TP53*wt were the oldest (median: 72 years; range: 31–94 years) followed by *PPM1D*mt/*TP53*mt (median: 71 years; range: 52–89 years), *PPM1D*wt/*TP53*wt (median: 69 years; range: 20–99 years), and *PPM1D*wt/

Figure 1: Variant allele frequency-based clonal analysis.





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	Dominant	Co-dominant	Sub-clone
t-CH	30 (56.6%)	15 (28.3%)	8 (15%)
CH	2 (28.6%)	1 (14.2%)	4 (57.1%)
t-CCUS	44 (47.8%)	18 (19.5%)	30 (32.6%)
CCUS	22 (53.6%)	5 (12.1%)	14 (34.1%)

Figure 1: Variant allele frequency-based clonal analysis (Continued).

A–B) Heatmaps showing VAFs of somatic mutations in patients with (**A**) CH (n=58) and (**B**) CCUS (n=137), categorised by clonal hierarchy: dominant (red), co-dominant (yellow), and sub-clonal (grey).

C) Bar chart comparing the proportion of dominant, co-dominant, and sub-clonal mutations across four groups: t-CH, CH, t-CCUS, and CCUS.

D) Table summarising the percentage of patients within each group who carried dominant, co-dominant, or sub-clonal mutations.

CCUS: clonal cytopenia of undetermined significance; CH: clonal haematopoiesis; t: therapy-related; VAF: variant allele frequency.

*TP53*mt (median: 65 years; range: 52–75 years) groups (p=0.004). Consistent with the notion that DNA damage response gene mutations are preferentially selected under the pressure of anticancer therapy,[3] the *PPM1D*mt/*TP53*wt genotype group were most frequent in therapy-related (t) CH/CCUS (80%, 66.5%, 76.5%, and 19%; p<0.001) and had a shorter time interval from last therapy to diagnosis (6.2, 5.9, 11.25, and 24.5 months; p<0.001) compared to *PPM1Dmt/TP53wt, TP53mt/PPM1Dwt*, and *TP53wt/PPM1Dwt,* respectively. A significantly higher proportion of patients in the *PPM1D*mt/*TP53*wt (6%/26%) and *PPM1D*mt/*TP53*mt (24%/24%) groups, in comparison to the *PPM1D*wt/*TP53*mt (0%/0%) and *PPM1D*wt/*TP53*wt (0%/3%) groups, received poly ADP-ribose polymerase inhibitors and radioisotope-based cytotoxic therapy, respectively (p=0.01; p<0.001). To describe the position of *PPM1D* mutations within the clonal architecture, the authors performed a VAF-based analysis to infer clonal hierarchy.[5] For this analysis, the authors compared individuals according to disease category and included 58 patients with CH and 137 patients with CCUS. Dominant *PPM1D* mutations were observed in 32 (53%) patients with CH, and 66 (50%) patients with CCUS (Figure 1A–B).

To further assess whether prior cytotoxic therapy influences the clonal position of *PPM1D* mutations, the authors stratified each disease group by therapy-related versus sporadic cases, and compared the distribution of dominant, co-dominant, and sub-clonal *PPM1D* mutations (Figure 1C–D). In the CH subgroup, prior therapy was associated with a higher likelihood of having a dominant *PPM1D* mutation (56%) than for sporadic cases (28%). The overall distribution of clonal categories differed significantly between therapy-related and sporadic CH (χ^2=6.83; degrees of freedom=2; p=0.033; Figure 1C–D). In CCUS, there was no significant difference in clonal status distribution by therapy exposure. Dominant mutations were seen in 44 (48%) therapy-related cases and 22 (53%) sporadic cases, co-dominant in 18 (20%) and five (12%), and sub clonal in 30 (32%) and 14 (34%), respectively (χ^2=1.11; degrees of freedom=2; p=0.58).

CONCLUSION

The authors acknowledge the limitations of their study, including shorter follow-up in the *PPM1D*mt/*TP53*wt and *PPM1D*mt/*TP53*mt groups, as well as heterogeneity in genomic sequencing techniques between the five academic institutions that participated in this study. However, to the best of their knowledge, this work represents the largest series reporting on the spectrum of precancerous *PPM1D* mutations in the context of evolving cancer therapies. In conclusion, while *PPM1D* mutations were frequently identified in t-CH/CCUS and associated with unexplained cytopenias in the context of low VAF, within limitations of a short follow-up in our cohort, they were associated with a low rate of myeloid clonal evolution, even in the presence of *TP53*mt. Longer-term follow-up is planned to better assess impacts on progression free survival and overall survival.

References

1. Badar T et al. Prognostic impact of 'multi-hit' versus 'single-hit' TP53 alteration in patients with acute myeloid leukemia: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases. Haematologica. 2024;109(11):3533-42.
2. Badar T et al. PPM1D somatic mutations in myeloid neoplasms: clinical profile, clonal characteristics and impact of concurrent somatic TP53 mutations. Blood. 2024;144(Suppl 1):3218.
3. Hsu JI et al. PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. Cell Stem Cell. 2018;23(5):700-13.e6.
4. Badar T et al. Spectrum, prevalence and clinical correlates of PPM1D mutations in patients with therapy related clonal hematopoiesis and clonal cytopenias. Poster PS1635. EHA Congress, 12-15 June, 2025.
5. Awada H et al. Clonal hematopoiesis-derived therapy-related myeloid neoplasms after autologous hematopoietic stem cell transplant for lymphoid and non-lymphoid disorders. Leukemia. 2024;38(6):1266-74.