SUBCLONAL AND CLONAL PROGRESSION OF PREVIOUSLY CHARACTERIZED MUTATIONS AND VARIANTS OF UNKNOWN SIGNIFICANCE (VUS) ACROSS A COHORT OF PLASMA CELL DYSCRASIA PATIENTS

K.EZELL[1], O. STECZKO[1], S.L. GODIN[1], V. OSADCHYI[1], K. MELEVEEDU[2] and S. KUMAR[2]

1. University of Connecticut, Department of Medicine, Farmington, CT, USA
2. UConn Health, Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, USA

22nd Annual MEETING & EXPOSITION
September 17-20, 2025 • Toronto, Canada
International Myeloma Society

INTRODUCTION

- Plasma cell dyscrasias (PCD) are genetically diverse
- Key oncogenic drivers in multiple myeloma (MM) have been identified, such as subclonal RAS mutations and TP53
- Few markers predict MGUS or smoldering MM progression
  - Current research targets mutational burden, cytogenetic shifts, and clonal diversity
  - Subclonal diversity may signal progression and resistance
- Variant allele frequency (VAF) serves as a clonality proxy; higher VAF indicates founder clones and lower VAF (<10%) suggests subclones

AIM

- To assess for clonal patterns and evolution across reported VUS and oncogenic mutations in a PCD cohort
- To determine if, in line with current thinking, subclonal diversity is seen more readily in malignant samples

METHOD

- We analyzed genomic variants from 252 PCD samples using the Tempus xT® 648-gene NGS panel
- NGS reports were digitized as sample-specific CSVs and analyzed using
  - Python in Jupyter (v7.3.2)
  - Excel (v16.96.1)
  - COSMIC (v102) web platform identified cancer-associated single nucleotide variants (SNVs)

RESULTS

- In 252 samples, 376 genes were identified as mutated
  - VUS were most common, comprising 322 genes
  - Oncogenic (potentially actionable or biologically relevant) mutations occurred in 81 genes
- Samples collected from Jan 2020 to May 2025 included
  - bone marrow (n=228)
  - tissue(n=5)
  - blood (n=19)
- Diagnoses confirmed by chart review included
  - MGUS (n=84)
  - SMM (n=23)
  - MM (n=102)
  - AL amyloidosis (n=14)
  - other PCDs (n=29)

- Mean VAF for all oncogenic genes (256 identified SNVs in total) was 15.7%, significantly lower than the mean VAF for all VUS genes (1123 SNVs in total) of 36.8% (Welch's t-Test, p<0.0001)

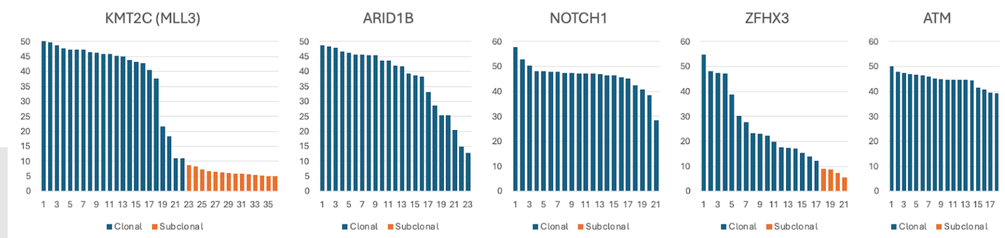

Figure 1a. Most common VUS genes by SNV VAF % where the x-axis represents number of SNVs and the y-axis represents the VAF % of each

- All ARID1B, NOTCH1, and ATM SNVs were clonal (VAF>10%)
- Of 19 ARID1B SNVs, 12 have not been previously associated with any cancer; only one (c.1016_1021dup) was previously linked to hematologic malignancy
- Seven of 12 NOTCH1 and 3 of 11 ATM SNVs were not previously reported
- Among clonal VUS, the malignant cohort harbored 217 unique genes (574 SNVs; 399 unique)
- Mean SNVs per gene were higher in malignant samples (1.44 vs. 1.09, p<0.0001)

- Mean VAF was higher in VUS versus oncogenic groups across malignancy status (One-way ANOVA p<0.0001 then Tukey's test with Benjamini-Hochberg adjusted p-values).
- VAF did not differ between oncogenic premalignant and malignant samples (p=0.9848).

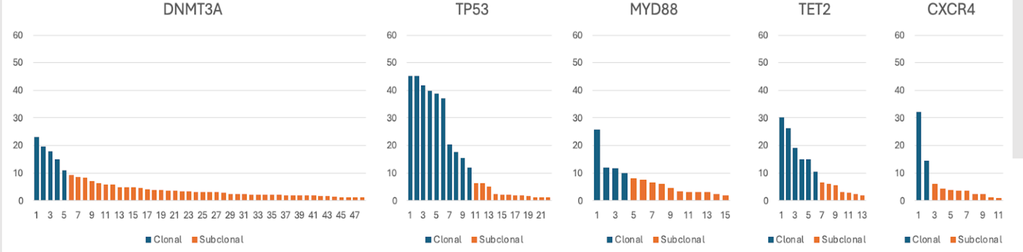

Figure 1b. Most common oncogenic (potentially actionable/biologically relevant) genes by SNV VAF %

- The malignant cohort had higher oncogenic mutations per sample than the premalignant cohort (Welch's t-test, p<0.0001), though VUS counts did not differ significantly (p=0.2276).

CONCLUSIONS

- Our analysis reveals distinct clonal patterns and mutational profiles across PCDs
  - Subclonal oncogenic mutations were more common in malignant states, while VUS were often clonal
  - VAF was overall lower in oncogenic mutations regardless of malignancy status
  - Oncogenic mutations were seen more often in malignant samples, however VUS mutations occurred at similar rates regardless of malignancy status
- Further studies on longitudinal clonal dynamics are needed

REFERENCES

1. Morgan GJ, et al. The genetic architecture of multiple myeloma. Nat Rev Cancer. 2012;12(5):335–48.
2. Maura F, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. Nat Commun. 2019;10(1):3835
3. Bolli N, et al. A new tool to predict the risk of progression in smoldering multiple myeloma based on mutational profiling. Blood Adv. 2020;4(20):4991–99.
4. Keats JJ, et al. Clonal competition with alternating dominance in multiple myeloma. Blood. 2012;120(5):1067–76.
5. Mikhael JR, et al. Interpretation of next-generation sequencing in myeloma. Blood Rev. 2021;47:100777.
6. Bustoros M, et al. Genomic profiling of smoldering multiple myeloma identifies patients at a high risk of disease progression. Nat Commun. 2020;11(1):1–9.
7. Dutta AK, et al. Subclonal evolution in disease progression from MGUS/SMM to multiple myeloma is characterised by clonal stability. Leukemia. 2019;33(2):457-468.

CONTACT INFORMATION

ezell@uchc.edu