

Genome Sequencing to Discover Drivers of Clonal Expansion in Smoldering Multiple Myeloma

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INTRODUCTION

Monoclonal Gammopathy of Undetermined Significance (**MGUS**) and Smoldering Multiple Myeloma (**SMM**) are heterogeneous diseases with overall rates of progression to Multiple Myeloma (**MM**) of 1% to 10% per year.

Whether any mutations are sufficient to cause, or instead prevent progression, remains an open fundamental question.

Better prediction models are required to identify patients who will benefit from early intervention therapy.

We leveraged whole-genome sequencing (**WGS**) in a large cohort of precursor patients to discover drivers of disease growth and monitor malignant transformation to multiple myeloma (MM).

KEY POINTS

- A reference map for genetic drivers of Multiple Myeloma and its precursor conditions
- Cancer drivers serve as tumor-based genomic biomarkers for the prediction of progression to MM

METHODS

WGS was performed on tumor and normal cells from 141 untreated patients with MGUS and SMM after written informed consent for research use (PCROWD study; IRB #14-174).

WGS dataset was combined with genomic data from the literature totaling 1,034 patients with WGS and/or exomes sampled across MM stages for comparative analysis and biomarker discovery (Fig. 1).

MutSig2CV, GISTIC2, and a novel method for structural variants were used to establish the list of candidate drivers across disease stages.

Longitudinal WGS data were analyzed with the PhylogeneticNDT suite of tools to characterize clonal evolution over time.

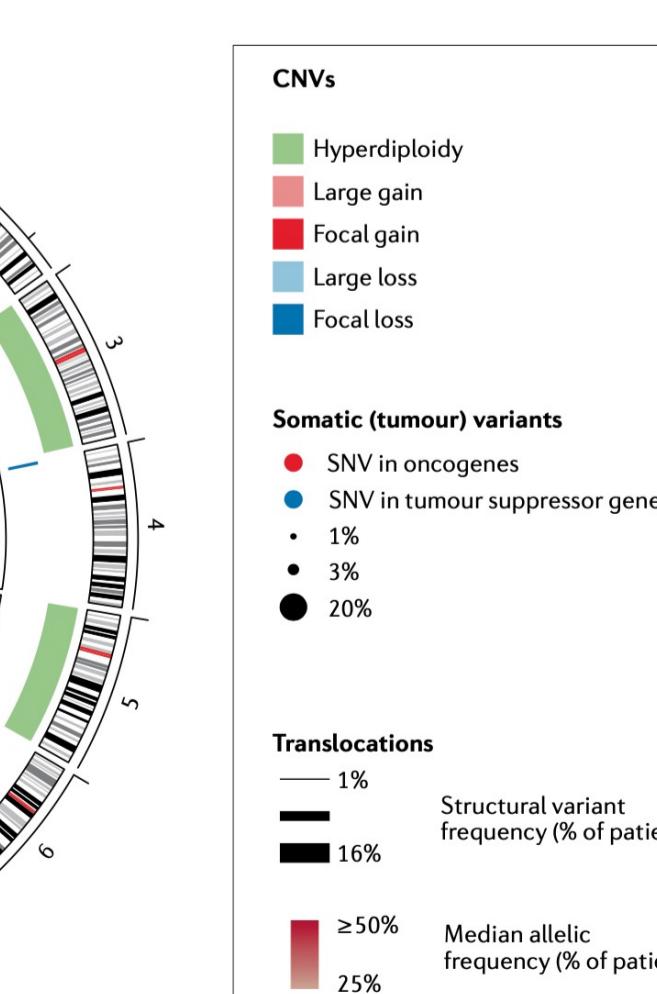


Fig. 1 | Overview of genome abnormalities in newly diagnosed multiple myeloma.

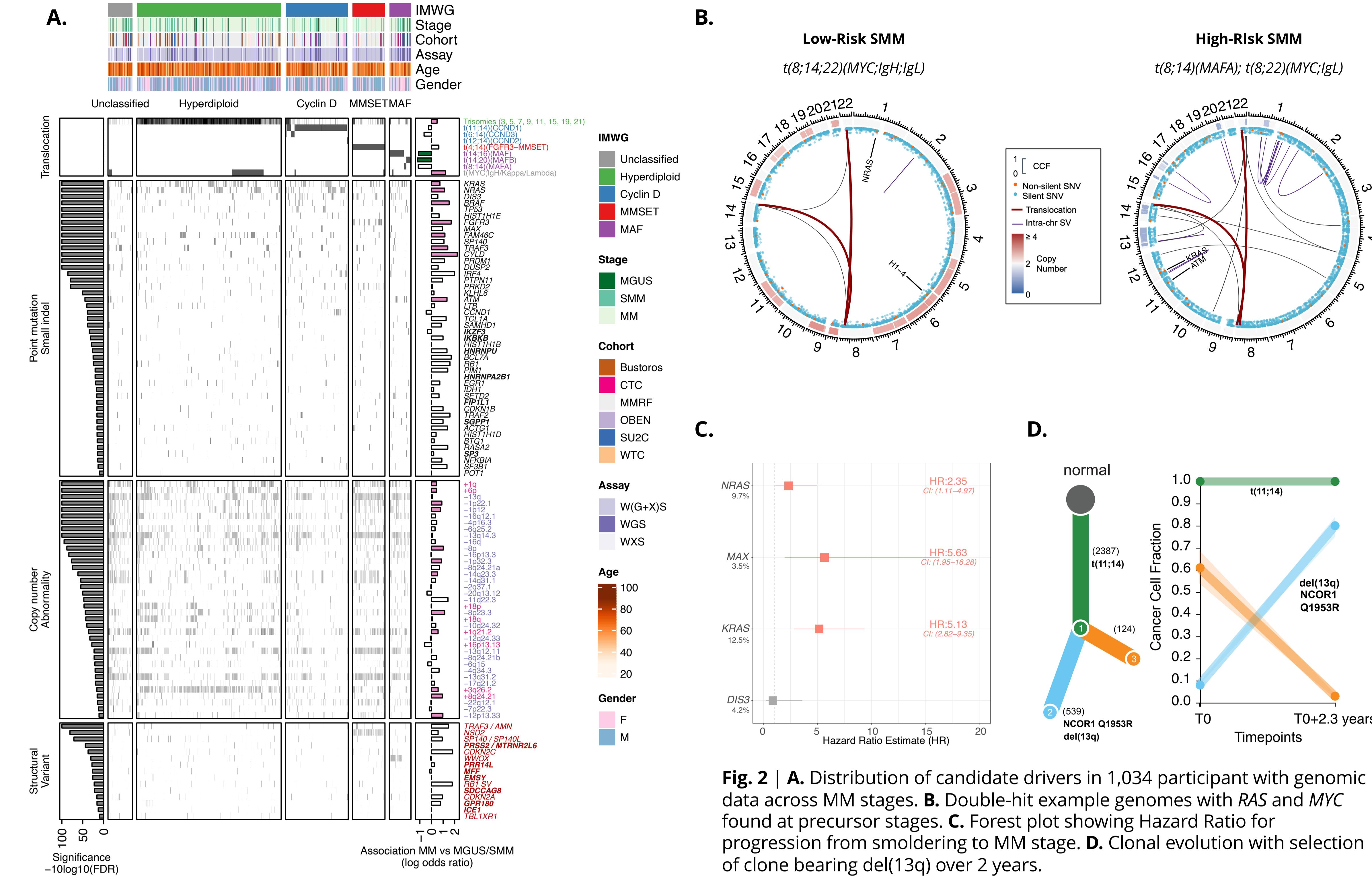


Fig. 2 | A. Distribution of candidate drivers in 1,034 participant with genomic data across MM stages. B. Double-hit example genomes with RAS and MYC found at precursor stages. C. Forest plot showing Hazard Ratio for progression from smoldering to MM stage. D. Clonal evolution with selection of clone bearing del(13q) over 2 years.

RESULTS

Patients were followed for a median time of 20 months from the sample date (range: 3 to 78 months), during which 11 progressed.

A validation cohort comprising 61 SMM with a median follow-up time of 36 months (range: 5 to 121), with 22 progressions was used to corroborate our findings.

In addition to known MM drivers KRAS, NRAS, DIS3, FAM46C, 16 new candidate genes were found significantly mutated, including IKZF3 (*Aiolos*) and across indolent stages (Fig. 2A-B).

Four regions with focal gains including chr(16p13)(**BCMA**) showed higher expression of candidate target with broad gain (e.g. **BCMA**: p=8.8E-3) and focal amplification (e.g. **BCMA**: p=6.2E-5), highlighting novel candidate targets for MM.

Mutants in **KRAS** were found in all disease risk groups and associated with progression to overt myeloma **Hazard Ratio: 5.1, CI_{95%}: [2.8, 9.4], q=4E-7** (Fig. 2C).

In one patient with serial sample acquisition over ≥ 2 years, emergence of high-risk, del(13q), NCOR1 mutant subclone (Fig. 2D) from 8 to 80% cancer cell fraction could be detected and modeled, with simultaneous extinction of orange subclone.

CONCLUSIONS

Precise integration of early- and late stage of MGUS, SMM, and MM allows discovery of novel cancer driver candidates.

These results highlight the power of genomic profiling in MM for early detection, discovery of novel drivers, monitoring of clonal selection and transformation to malignant disease.

We show SMM is not a simple genetically-mature disorder, but rather a heterogeneous state with MM features, which could be leveraged for therapeutic interventions.

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