nature reviews
disease primers

Chromosomal abnormalities in multiple myeloma

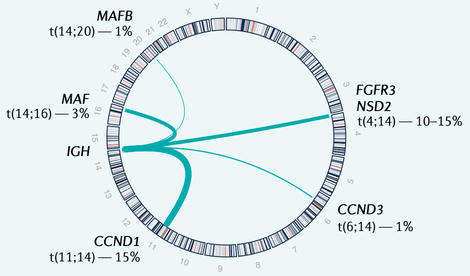
Aneta Mikulasova, Gareth J. Morgan and Brian A. Walker

Multiple myeloma (MM) is a malignancy of post-germinal centre (GC) B cells called plasma cells and accounts for ~2% of all new cancer cases (https://seer.cancer.gov/statfacts/html/mulmy.html). The accumulation of plasma cells in the bone marrow results in bone lesions and high levels of clonal immunoglobulin in the blood. As such, patients present with the clinical symptoms of hypercalcaemia, renal impairment, anaemia and/or bone disease. MM is preceded by two asymptomatic stages known as monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) where the clonal immunoglobulin is detected but generally there is no therapeutic intervention.

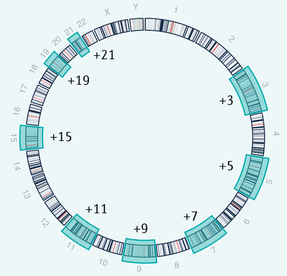
MM cells have undergone class-switch recombination (CSR) and somatic hypermutation (SHM) in the GC. The plasma cells acquire initiating primary genomic events (*IGH* translocations or hyperdiploidy) in the GC and accumulate secondary events such as complex structural events, copy number abnormalities and mutations, which advance the disease through the asymptomatic stages of MGUS and SMM to symptomatic MM. As the disease progresses, cells proliferate and expand and genomic instability increases, which results in the accumulation of genomic diversity. Spread of cells throughout the skeleton gives rise to the independent evolution of clones and a focal growth pattern. Treatment creates an evolutionary bottleneck where resistant cells can expand, leading to relapse.

Initiating copy number and structural events[1,2]

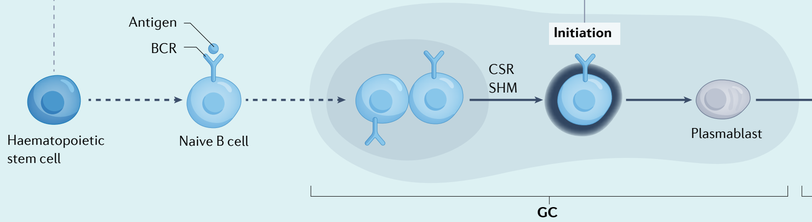
Canonical *IGH* translocations (40%) that occur in >1% of newly diagnosed patients



Hyperdiploidy (50%)



Predisposition
Germline mutations in *ULK4*, *TRAK1*, *DNMT3A*, *DNAH11*, *CDCA7L* and *DIS3*



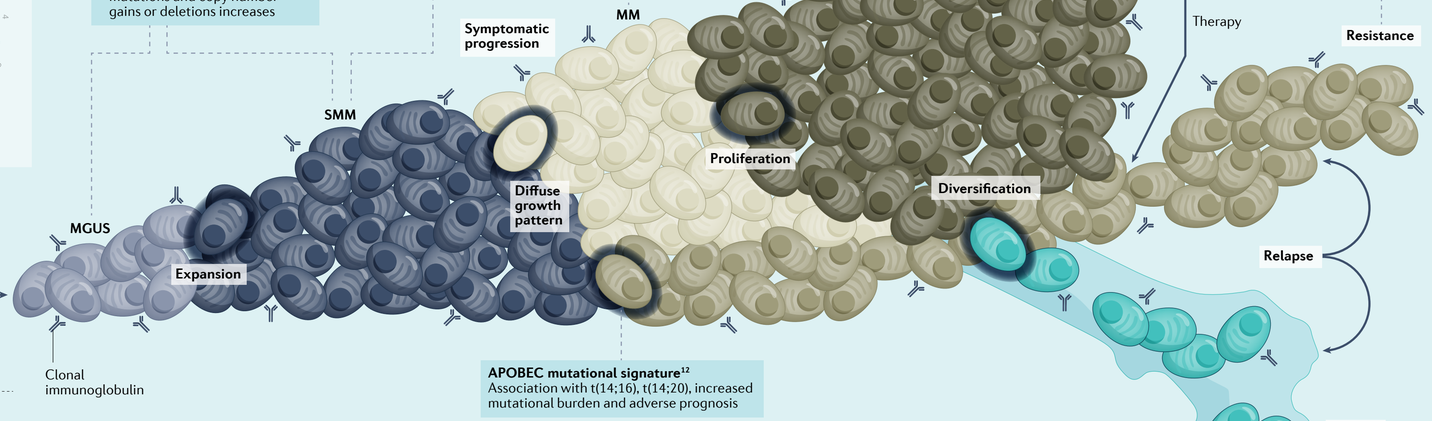
MGUS[3] and SMM
- In MGUS, cells contain mutations but not always gains or deletions of chromosomes
- Mutation rate is low and can persist for decades
- In SMM, the frequency of mutations and copy number gains or deletions increases

High-risk SMM[4,5]
Molecular high-risk events defining the transition to MM include t(*MYC*) and mutations in
- *KRAS* and *NRAS* (involved in Ras signalling), *TP53*, *ATM* and *ATR* (involved in DNA repair) and *DIS3* and *TENT5C* (involved in RNA processing)

MM driver events[6]
Driver events confer a growth advantage to cells. The most frequently mutated genes include
- *KRAS* (22%), *NRAS* (17%), *DIS3* (10%), *TENT5C* (9%), *BRAF* (8%) and *TP53* (6%)

High-risk events[7]
High-risk events associated with disease progression and poor prognosis include
- t(4;14), t(14;16) and t(14;20)
- Biallelic alteration of *TP53*
- Gain or amplification of 1q

Resistance events[8,9]
Genomic events linked to treatment resistance
- *CRBN* variants in immunomodulatory imide drug resistance
- Deletion of immunotherapy targets, for example *TNFRSF17* and anti-BCMA



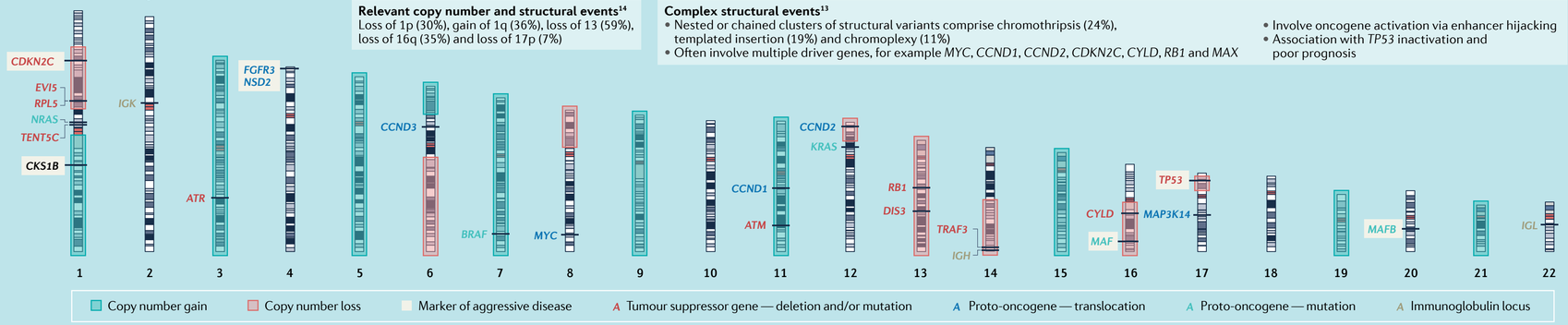
APOBEC mutational signature[12]
Association with t(14;16), t(14;20), increased mutational burden and adverse prognosis

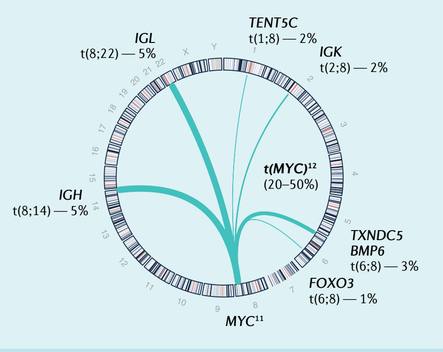
Focal lesions[10]
Associated with
- Increased clonal diversity
- Generation of resistance
- Excess contribution to relapse

Overview of common genetic abnormalities in MM

Relevant copy number and structural events[14]
Loss of 1p (30%), gain of 1q (36%), loss of 13 (59%), loss of 16q (35%) and loss of 17p (7%)

Complex structural events[13]
- Nested or chained clusters of structural variants comprise chromothripsis (24%), templated insertion (19%) and chromoplexy (11%)
- Often involve multiple driver genes, for example *MYC*, *CCND1*, *CCND2*, *CDKN2C*, *CYLD*, *RB1* and *MAX*
- Involve oncogene activation via enhancer hijacking
- Association with *TP53* inactivation and poor prognosis





Clonal evolution at each stage
- Increasing diversity
- Clonal competition
- Selective sweep

References

1. Walker, B. A. et al. Characterization of *IGH* locus breakpoints in multiple myeloma indicates a subset of translocations appear to occur in pregerminal center B cells. *Blood* **121**, 3413–3419 (2013).
2. Maura, F. et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. *Nat. Commun.* **10**, 3835 (2019).
3. Mikulasova, A. et al. The spectrum of somatic mutations in monoclonal gammopathy of undetermined significance indicates a less complex genomic landscape than that in multiple myeloma. *Haematologica* **102**, 1617–1625 (2017).
4. Boyle, E. M. et al. The molecular make up of smoldering myeloma highlights the evolutionary pathways leading to multiple myeloma. *Nat. Commun.* **12**, 293 (2021).
5. Bustoros, M. et al. Genomic profiling of smoldering multiple myeloma identifies patients at a high risk of disease progression. *J. Clin. Oncol.* **38**, 2380–2389 (2020).
6. Walker, B. A. et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood* **132**, 587–597 (2018).
7. Manier, S. et al. Genomic complexity of multiple myeloma and its clinical implications. *Nat. Rev. Clin. Oncol.* **14**, 100–113 (2017).
8. Gooding, S. et al. Multiple cereblon genetic changes are associated with acquired resistance to lenalidomide or pomalidomide in multiple myeloma. *Blood* **137**, 232–237 (2021).
9. Da Vià, M. C. et al. Homozygous *BCMA* gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat. Med.* **27**, 616–619 (2021).
10. Rasche, L. et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. *Blood* **132**, 59–66 (2018).
11. Mikulasova, A. et al. Microhomology-mediated end joining drives complex rearrangements and overexpression of MYC and *PVT1* in multiple myeloma. *Haematologica* **105**, 1055–1066 (2020).
12. Walker, B. A. et al. APOBEC family mutational signatures are associated with poor prognosis translocations in multiple myeloma. *Nat. Commun.* **6**, 6997 (2015).
13. Rustad, E. H. et al. Revealing the impact of structural variants in multiple myeloma. *Blood Cancer Discov.* **1**, 258–273 (2020).
14. Walker, B. A. et al. A compendium of myeloma-associated chromosomal copy number abnormalities and their prognostic value. *Blood* **116**, e56–e65 (2010).

The poster content is peer reviewed, editorially independent and the sole responsibility of Springer Nature Limited.

Edited by Louise Adams; copyedited by Rebecca J. Hill; designed by Laura Marshall.

https://www.nature.com/articles/s4XXXX-019-0XXX-?

Affiliations

Aneta Mikulasova is at Biosciences Institute, Newcastle University, Newcastle upon Tyne, UK. aneta.mikulasova@newcastle.ac.uk
Gareth J. Morgan is at NYU Langone Medical Center, Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA. gareth.morgan@nyulangone.org
Brian A. Walker is at Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology Oncology, Indiana University, Indianapolis, IN, USA. bw75@iu.edu

Competing interests

B.A.W. receives research funding from the Leukemia & Lymphoma Society, Bristol Myers Squibb, and Genentech and has received consultation fees from Genentech and Sanofi. G.J.M. has unpaid advisory positions for Bristol Myers Squibb, Sanofi, Karyopharm, Janssen, GlaxoSmithKline, Amgen, Oncopeptides, and AbbVie. A.M. declares no competing interests.