Genomic complexity of multiple myeloma and its clinical implications

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Abstract | Multiple myeloma (MM) is a genetically complex disease that evolves from pre-malignant stages, such as monoclonal gammaopathy of undetermined significance and smouldering multiple myeloma, and progresses to symptomatic MM; this continuum provides a unique framework to study the sequential genomic evolution of MM. In the past 5 years, results from large-scale whole-exome sequencing studies have provided new insights into the clonal heterogeneity and evolution of the disease. Moreover, the recurrent co-occurrence of genomic events helps to dissect the genomic complexity underlying tumour progression. According to the primary genetic events involved in tumorigenesis, MM tumours are hierarchically subdivided into hyperdiploid and non-hyperdiploid subtypes; subsequently, secondary genetic events lead to tumour progression. In this Review, we describe the 'driver' gene alterations involved in the development and progression of MM, with a focus on the sequential acquisition of the main genomic aberrations. We also provide valuable insight into the clonal heterogeneity and clonal evolution of the disease, as well as into the therapeutic implications of a comprehensive understanding of the genomic complexity of MM.

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Multiple myeloma (MM) is a haematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow[1]. In the USA, the prevalence of MM was estimated to be 89,650 people in 2012, with an annual incidence of 6.3 new cases per 100,000 individuals[2]. In 2012, MM represented 1.6% of all cancers and was the second most frequent haematological malignancy in the USA[2]. MM predominantly affects elderly people, and the median age at diagnosis is 69 years[2]. Traditionally, this disease was associated with a poor prognosis, with a 5-year overall survival of 48.5% (according to data from 2006–2012)[2]; however, the introduction of new-generation proteasome inhibitors and immunomodulatory drugs, as well as new potent monoclonal antibodies has greatly improved the clinical outcome of patients with MM.

Similarly to other cancer types, MM is a genetically complex and heterogeneous disease resulting from multiple genomic events that lead to tumour development and progression. One of the unique features of MM, however, is the presence of well-defined pre-malignant states termed monoclonal gammaopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM)[3,4]. In virtually all patients, a small-size pre-malignant clone is detectable by serum protein electrophoresis before the development of overt disease that will continue to acquire more genomic abnormalities as it progresses toward MM. One of the pivotal aspects in cancer is the temporal sequence in which genetic aberrations arise. Thus, a clinical model of the disease continuum between MGUS, SMM and MM provides a unique framework to understand the genomic hierarchy, as well as the clonal heterogeneity and clonal evolution underlying MM.

This sequence of genomic aberrations begins with germline events that predispose to the disease, followed by early — and likely initiating — events, before the later acquisition of genomic aberrations that ultimately lead to disease progression and resistance to treatment. Hence, genetic events detected at the MGUS stage are likely to be primary events involved in tumour development. By contrast, events present at the MM stages that were absent in MGUS are probably secondary events leading to tumour progression. Analytical tools enabling the deconvolution of clonal heterogeneity within a single patient can be used to gain a better understanding of the temporal sequence of genomic events in MM tumours.

Although valuable genomic information had been derived from studies using fluorescence *in situ* hybridization (FISH), karyotyping and targeted-sequencing studies, results from large-scale whole-exome sequencing (WES) studies in cohorts of patients with MM

Key points

- The development of multiple myeloma is preceded by pre-malignant stages, and therefore constitutes a well-defined model of disease progression that is appropriate for studies of clonal evolution and heterogeneity
- Whole-exome sequencing studies have enabled the characterization of the genomic alterations underlying the pathogenesis of multiple myeloma
- The primary genomic events involved in multiple myeloma are the acquisition of hyperdiploidy or translocations affecting the *IGH* genes; these events are mutually exclusive
- Secondary genomic events include chromosomal translocations, copy-number variations and single-nucleotide variants
- Genomic events underlying multiple myeloma affect multiple signalling pathways including the MYC, NF-κB, and MAPK pathways, plasma-cell differentiation, cell-cycle regulation or DNA-damage repair

published in the past 5 years have led to a new appreciation of the genomic landscape of the disease[5–9]. Primary events are usually divided into hyperdiploid (HRD) and non-HRD subtypes. HRD tumours are characterized by the presence of trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19, and/or 21. Non-HRD tumours harbour translocations affecting the genes encoding immunoglobulin (Ig) heavy chains (*IGH*) — mainly t(4;14), t(6;14), t(11;14), t(14;16) and t(14;20)[8]. Secondary events provide a fitness advantage to a particular subclone over other populations, and are required for tumour progression. For example, most of copy-number variations (CNV), translocations involving *MYC,* and somatic mutations affecting MAPK, NF-κB, and DNA-repair pathways are observed during MM, and less frequently in pre-malignant stages; therefore, these events are likely to be secondary driver events. In this Review, we dissect the genomic landscape of MM in light of large-scale WES studies ($n \approx 750$ patients) published in the past 5 years. We define the driver genomic events in MM and their sequence of acquisition, as well as the clonal heterogeneity of MM and its implications for both clonal evolution and clinical outcomes.

Inherited variants in MM development

Germline genetic information provides an important contribution to the likelihood of developing cancer, which is variable among different cancer types. Relatives of individuals with MM have a 2–4-fold elevated risk of developing the disease[10], thus confirming a strong germline contribution. Studies of large-scale genomic variants to define inherited predisposition can, therefore, provide valuable information on the oncogenesis of this disease and, ultimately, help identify new therapeutic targets.

Genome-wide association studies (GWAS) with results published in 2012–2013 (REFS 11, 12) have examined germline single-nucleotide polymorphisms (SNPs) associated with MM in >4,600 patients with this disease and in 10,990 healthy individuals. To date, these studies have identified seven genetic loci associated with a modest but increased risk (odds ratio >1) of developing MM[12] (TABLE 1). These seven loci contribute to inherited genetic susceptibility to MM, and collectively account

for ~13% of the familial risk of MM. The complete functional role of these candidate genes remains to be elucidated, as the authors found no association between the presence of specific variant forms of these SNPs and the expression levels of the related genes in cells derived from patients with MM. Importantly, these seven loci were also found to be associated with an increased risk of developing MGUS[13], which indicates an early role for these inherited genetic susceptibilities in the development of pre-malignancies.

Other susceptibility loci have been associated with specific molecular subgroups of MM. Subsequent analysis[14] of the samples used in the two previous GWAS studies[11,12] revealed that the variant rs603965 maps to a region of linkage disequilibrium at 11q13.3 and is responsible for the c.870G>A polymorphism in *CCND1* (encoding cyclin D1). Moreover, the translocation t(11;14)(q13;q32), which places *CCND1* under the control of the *IGH* enhancer, is frequently coincident with the c.870G>A polymorphism[14], providing an interesting example of an interaction between a constitutive genetic locus (rs603965) and a somatic variation in MM affecting *CCND1*.

Strikingly, some inherited risk loci have particular associations with specific disease phenotypes. For example, a locus at 8q24.12 (rs4407910 in *TNFRSF11B*) is positively associated with the development of MM bone disease (such as osteolytic lesions)[15]. *TNFRSF11B* (commonly referred to as *OPG*) encodes a negative regulator of bone resorption, osteoprotegerin, that acts as a decoy receptor for the product of *TNFSF11* (commonly referred to as RANKL). Another locus at 5q15 (rs56219066T in *ELL2*) is associated with susceptibility to MM[16]; *ELL2* encodes an elongation factor that is part of the super-elongation complex involved in the metabolism of immunoglobulin mRNA in plasma cells. Interestingly, the presence of the *ELL2* risk allele is also associated with lower levels of IgA and IgG in healthy individuals, compared with individuals in whom this specific allele is absent, and irrespectively of MM[16]. Another example is the positive association between a locus at 16p13 (rs72773978 in *FOPNL*) and the survival of patients with MM[17]. On the basis of these studies[16,17], more susceptibility loci are likely to be identified in the future and might enable the identification of patients at risk of developing MM. For example, it has been reported that African-American populations have a higher risk of developing MM than White populations[18], but no genetic variants related to this dissimilarity have been identified to date.

Chromosomal translocations

Somatic hypermutation and class-switch recombination, two key features of B-cell development that serve as a physiological mechanism of affinity maturation in the germinal centre, are also involved in the ontogeny of MM[19]. Both processes require the expression of single-stranded DNA cytosine deaminase (encoded by *AICDA*, commonly referred to as *AID*) and involve the generation of double-strand DNA breaks in the loci encoding Ig. Aberrant recombination can occur during

Table 1 | **Inherited variants associated with multiple myeloma**

Variant and risk allele involved	Chromosomal location	Genes involved	OR (range)	Associated risk
rs4487645C[11–13]	7p15.3	Surrounded by *DNAH11* and *CDCA7L*	1.38 (95% CI 1.28–1.50)	Transition from MGUS to MM
rs1052501G[11–13]	3p22.1	*ULK4*	1.32 (95% CI 1.20–1.45)	Transition from MGUS to MM
rs6746082A[11–13]	2p23.3	Surrounded by *DNMT3A* and *DTNB*	1.29 (95% CI 1.17–1.42)	Transition from MGUS to MM
rs10936599G[11–13]	3q26.2	Surrounded by *MYNN* and *TERC*	1.26 (95% CI 1.18–1.33)	Transition from MGUS to MM
rs2285803A[11–13]	6p21.3	*PSORS1C2*	1.19 (95% CI 1.13–1.26)	Transition from MGUS to MM
rs4273077G[11–13]	17p11.2	*TNFRSF13B*	1.26 (95% CI 1.16–1.36)	Transition from MGUS to MM
rs877529A[11–13]	22q13.1	*CBX7*	1.23 (95% CI 1.17–1.29)	Transition from MGUS to MM
rs603965A[14]	11q13.3	*CCND1*	1.82 (95% CI 1.52–2.19)	t(11;14) in MM
rs4407910 (REF. 15)	8q24.12	*OPG*	1.38 (95% CI 1.24–1.54)	MM bone disease (osteolytic lesions)
rs56219066T[16]	5q15	*ELL2*	1.23 (95% CI 1.14–1.33)	MM
rs72773978T[17]	16p13.11	*FOPNL*	2.65 (95% CI 1.94–3.58)	MM prognosis

MGUS, monoclonal gammaopathy of undetermined significance; MM, multiple myeloma; OR, odds ratio; rs, refSNP number; t, translocation.

class-switch recombination and result in chromosomal translocations, one of the central characteristics of MM.

In MM, the large majority (>90%) of chromosomal translocations affect chromosome 14, specifically the *IGH* locus at 14q32.33, which is one of the most heavily transcribed genes in plasma cells[19]. Therefore, in the resulting fusion product, partner genes are under the control of the *IGH* enhancer, and the expression of specific oncogenes (such as *MMSET/FGFR3*, *CCND3*, *CCND1*, *MAF*, and *MAFB* in translocations t(4;14), t(6;14), t(11;14), t(14;16), and t(14;20), respectively) is upregulated, imparting a selective advantage to subclones harbouring these translocations. All of these translocations probably lead to deregulation of cyclin D expression, and resultant cell-cycle G1/S transition, which has been described as one of the key early molecular abnormalities in MM[20]. Interestingly, a study in patients with MM found significant correlations between ageing and a decreased frequency of translocations affecting *IGH* ($P = 0.001$), and an increased frequency of HRD ($P = 0.004$)[21]. These translocations are also detectable in MGUS, consistent with their early occurrence in MM oncogenesis[22–24]. Strikingly, results from a 2015 study[8] suggest that most of the translocation partner genes are mutated in 10–25% of patients, probably as the result of somatic hypermutation events mediated by *AID* on the derivative chromosome der(14)[8] (FIG. 1). Functional validation of these partner mutations is required, however, to understand whether they represent true driver mutations or 'passenger' events.

Translocation (11;14). The t(11;14) translocation is the most frequently detected alteration in patients with MM (prevalence of ~15–20%)[8,25]. This translocation induces an upregulation of *CCND1* expression by its juxtaposition to the *IGH* enhancer. Normally, B cells express cyclins D2 and D3, but not cyclin D1 (REFS 26, 27). The chromosomal breakpoints seem to be located in the 5′

end of *CCND1* (REF. 28). The prognostic relevance of t(11;14) is considered neutral; however, a study published in 2015 reported that this translocation is associated with an activating mutation in *CCND1* in 10% of patients, and co-occurrence of these genetic alterations is associated with poor prognosis[8].

Translocation (4;14). The t(4;14) chromosome rearrangement is observed in ~15% of patients with MM[8] and has been associated with an adverse prognosis in a variety of clinical settings[29–33]. Juxtaposition with the *IGH* enhancer results in deregulation of the expression of *FGFR3* and *MMSET* (also referred to as *WHSC1*)[34]. The breakpoints are all located between *FGFR3* and *MMSET*, with fusions resulting in overexpression of *MMSET* in all patients, and of *FGFR3* in 70% of them[28,35,36]. *MMSET* is a methyltransferase protein, upregulation of which leads to increased methylation of histone H3K36, thus modulating the expression of several genes[37]. *MMSET* has also been shown to regulate methylation of histone H4K20, subsequently affecting the recruitment of p53-binding protein 1 (53BP1) at the site of DNA damage[38]. *FGFR3* is a tyrosine-kinase receptor that is activated by oncogenic mutations in several solid tumour types[39]. Of note, *FGFR3* mutations are detected in 17% of patients harbouring t(4;14), and probably result from somatic hypermutations on der(14). Interestingly, despite the poor prognosis associated with t(4;14), early treatment of these patients with the proteasome inhibitor bortezomib results in a survival improvement[40,41], warranting future studies on the use of proteasome inhibitors for the treatment of patients with MM.

Translocation (14;16). The t(14;16) translocation is estimated to be present in about 5% of patients with MM[8]. This translocation results in the overexpression of the *MAF* oncogenic splice variant c-MAF, a transcription
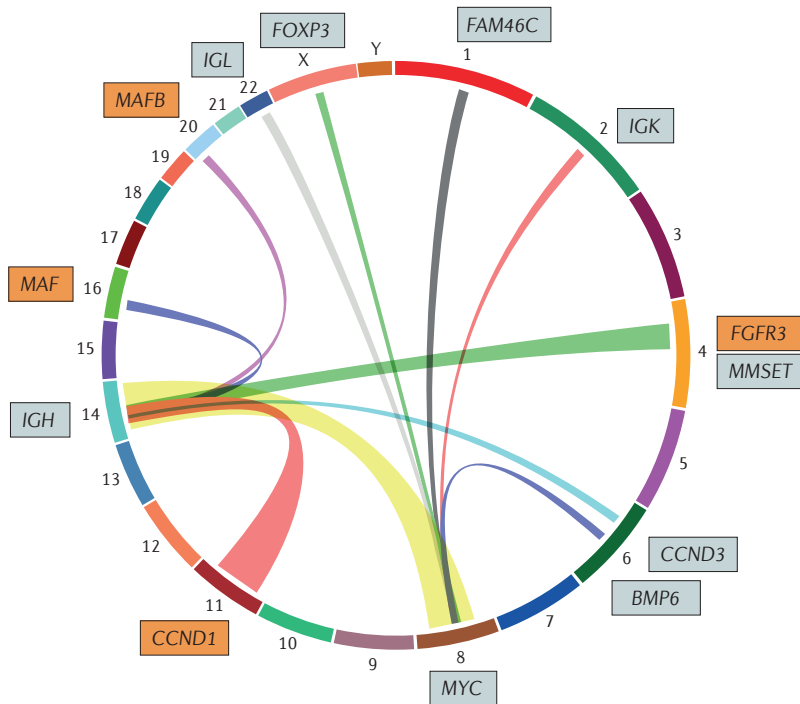
Figure 1 | **Translocations involved in multiple myeloma.** In this Circos plot, line thickness correlates with the frequency of the translocations. The plot is based on data from whole-exome sequencing — with baits on *MYC*, *IGH*, *IGL* and *IGK* loci — of tumour samples from 463 patients with newly diagnosed multiple myeloma[8]. The co-occurrence of partner gene mutations is indicated in orange.

factor that upregulates the expression of a number of genes (including *CCND2*) by binding directly to their promoter regions[42;43]. The breakpoints are located downstream of *MAF,* within the last exon of the neighbouring *WWOX* gene, a known tumour suppressor[28]. Mutations in *MAF* have been detected in 13% of patients with MM harbouring t(14;16)[8]. Interestingly, results from a study published in 2015 suggest that *MAF* upregulates expression of the DNA-editing enzymes *APOBEC3A* and *APOBEC3B* in MM tumours harbouring t(14;16), leading to a mutational pattern denominated APOBEC signature[8] and characterized by a high mutation rate[8]. The t(14;16) aberration has been associated with a poor prognosis in a number of clinical studies[31], although this translocation was not associated with a particular prognosis in a large analysis of 1,003 patients[44].

Translocation (6;14). The rare t(6;14) translocation, which is present in only ~1–2% of patients with MM[8,45], results in the juxtaposition of *CCND3* to the *IGH* enhancers, and therefore in the direct upregulation of *CCND3* expression[29,46]. The breakpoints are all located in the 5′ end of *CCND3* (REF. 26). To date, no mutations in *CCND3* affecting only patients harbouring t(6;14) have been reported[8]. The overall prognostic implication of this translocation is neutral[47].

Translocation (14;20). The t(14;20), the rarest of the five major translocation detected in patients with MM (present in ~1% of patients)[8], results in upregulation of the

expression of the *MAF* gene paralogue *MAFB*. According to microarray studies[27], *MAFB* overexpression results in a gene-expression profile similar to that associated with *MAF* overexpression[29], implying common downstream targets of both genes, such as *CCND2*. *MAFB* is mutated in 25% of patients with MM harbouring t(14;20)[9]. Tumours with t(14;20) have an APOBEC mutational signature[8], which is suggested to be caused by the upregulation of *APOBEC4* expression[8]. The t(14; 20) aberration is associated with a poor prognosis when detected after the onset of MM, but, paradoxically, with long-term stable disease when found in the MGUS and SMM stages[48].

Translocations affecting MYC. The five main translocations involving *IGH* are considered primary genomic events, whereas translocations that affect *MYC* are a secondary genomic event: these translocations are present in only 3–4% of patients with MGUS or SMM[49], but occur in 15–20% of patients with newly diagnosed MM[8,49,50]. Interestingly, the affected translocations are associated with kataegis, a specific pattern of localized hypermutation linked to deregulation of APOBEC activity, around the translocation breakpoints. Kataegis is believed to cluster next to junctions of chromosomal rearrangements because APOBEC operates on single-stranded DNA exposed at the translocation site before they are repaired[51]. The most common partner loci in translocations affecting *MYC* include the immunoglobulin (Ig)-encoding genes *IGH* (16.5%), *IGL* (16.5%) and *IGK* (6%), but also *FAM46C* (9.5%), *FOXO3* (6%) and *BMP6* (3.5%)[8]. In all situations, these translocations lead to a substantial overexpression of *MYC*, probably resulting from the juxtaposition of super-enhancers surrounding the partner gene to the *MYC* locus[8,52,53]. Translocations affecting *MYC* are frequently observed in HRD tumours (in about 65% of cases), and are inversely correlated with t(4;14)[9] (Bayesian inference correlation = −0.13). Translocations affecting *MYC* are associated with a poor outcome, specifically when they involve an Ig partner[8].

Copy-number variations
CNVs affecting MM span a wide spectrum of fragment sizes, from focal deletions or amplifications to chromosome-arm events or the common HRD MM genome. Similarly to single-nucleotide mutations, CNVs have been proposed to act both as driver and passenger events. Highly frequent and recurrent CNVs are probably driver events, suggesting that the minimally amplified or deleted regions contain important genes involved in the development and progression of MM[54–58] (FIG. 2).

Hyperdiploidy
In humans, HRD is defined as a number of chromosomes between 48 and 74. HRD is detected at diagnosis in about 50% of individuals with MGUS, SMM or MM, and is characterized by multiple chromosomal gains, preferentially trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19 and/or 21 (REFS 8,59–61). This level of genome-wide alterations prompts two important questions: first, about the potential mechanisms that would cause such large and concomitant genomic aberrations, and second, on
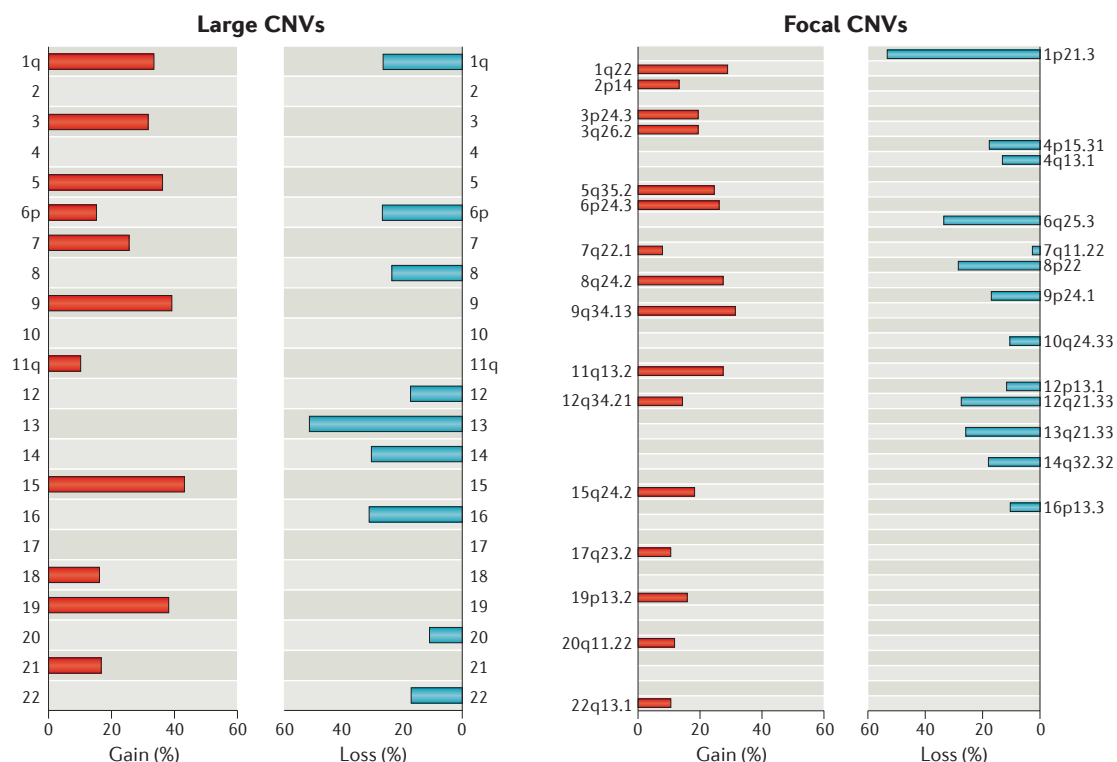
Figure 2 | **Copy-number variations in multiple myeloma. a** | Data provided are the average frequencies of recurrent chromosomal gain and loss reported in two studies in which single-nucleotide polymorphism (SNP) arrays were used to analyse samples from 114 (REF. 55) and 192 (REF. 76) patients with multiple myeloma. **b** | Frequency of focal changes in multiple myeloma. Data were obtained from a study using the GISTIC algorithm[89] to analyse samples from 153 patients[6]. CNVs, copy-number variations.

how the fitness advantage associated with these drastic genome-wide changes would be selected for in tumour initiation and evolution. The mechanism underlying HRD has not been well-established, but one hypothesis[60] suggests that the gain of multiple, whole chromosomes would occur during a single catastrophic failed mitotic event rather than through the serial gain of chromosomes over time[62]. Only a limited percentage of HRD tumours (<10%) have a concurrent primary translocation affecting *IGH*, but a positive correlation (Bayesian inference correlation = 0.14) exists between HRD and translocations affecting *MYC* — involving either *IGH* or another locus[8,63]. Interestingly, HRD can precede primary translocations affecting *IGH* in patients in whom such translocations concur with HRD, as revealed by studies using single-cell sequencing analysis[64]. In terms of signalling pathways, HRD tumours display biological heterogeneity: some patients' tumours harbour high expression levels of proliferation-associated genes, while others are characterized by aberrant expression of genes involved in the NF-κB signalling pathway, or by overexpression of *HGF* and *IL-6*, in equal proportions[65]. The survival outcomes of patients with abnormal karyotypes are less favourable than those of patients with normal karyotypes[64], but HRD is associated with more favourable survival outcomes than hypodiploidy (<45 chromosomes)[66]. Moreover, patients with HRD MM and coexistent adverse cytogenetic lesions (such as del(17p),

t(4;14) and gain of 1q) have worse survival outcomes than patients with HRD MM alone[64]. Evidence published in 2015 (REF. 65) indicates that, among patients harbouring HRD, only those with trisomy 3 or trisomy 5 had significantly better overall survival, whereas trisomy 21 was associated with a poor outcome[67].

Chromosome-arm events
Alterations involving entire chromosome arms are observed frequently in patients with MM. The increased characterization of focal amplifications or deletions, and of minimally amplified or deleted regions in the same locus helps to understand the oncogenic mechanisms underlying CNVs affecting chromosome arms. Herein, we discuss the most frequent among such alterations (FIG. 2).

1q gain. Around 35–40% of patients with MM harbour duplications of the long arm of chromosome 1 (REFS 53,66–69), which has been proposed to have an adverse effect on overall survival[68]. The mechanism underlying the amplification of 1q is believed to involve instability of the 1q12 pericentromeric region and 'jumping' translocations of the whole 1q arm, which could be linked with specific hypomethylation of the 1q12 pericentromeric region and, therefore, highly decondensed pericentromeric heterochromatin[69–71]. The resulting gain of 1q21 region, which can be detected with a specific

probe for *CKS1B*, is a prognostic factor independent from other adverse cytogenetic lesions and is frequently associated with gain of 1q and associated with poor outcomes of patients with MM[55,68]. The relevant driver genes present on 1q have not been fully explored, but a minimally amplified region containing 679 genes was identified between 1q21.1 and 1q23.3 (REFS 55, 68, 72). Among these genes, candidate oncogenes include *CKS1B*, *ANP32E*, *BCL9*, and *PDZK1*. ANP32E, a protein phosphatase 2A inhibitor involved in chromatin remodelling and transcriptional regulation, deserves particular interest because it has been shown to be independently associated with poor outcomes in patients with MM[55]. Of note, the number of 1q copies seems to be correlated with clinical outcome: patients harbouring at least four copies of 1q have a less favourable prognosis than patients harbouring three copies of 1q[9,73].

1p deletion. Approximately 30% of patients with MM harbour deletions of 1p, which are associated with a poor prognosis[55,74–76]. The deletion of two regions of the 1p arm, 1p12 and 1p32.3, is of interest in the pathogenesis of MM. 1p12 contains the candidate tumour suppressor gene *FAM46C*, expression of which has been positively correlated with ribosomal proteins and eukaryotic initiation and elongation factors involved in protein translation[5]. This gene has been shown to be frequently mutated in patients with MM (~10%) and is independently correlated with poor prognosis[5,55,74,77]. The 1p32.3 region can be hemizygously or homozygously deleted, and contains two genes, *CDKN2C* and *FAF1*. *CDKN2C* is a cyclin-dependent kinase 6 inhibitor involved in negative regulation of the cell cycle, whereas *FAF1* encodes a protein involved in initiation and enhancement of apoptosis through the FAS pathway. *CDKN2C* is homozygously deleted in 1.5% of patients with MM[6].

13q deletion. Monosomy of the long arm of chromosome 13 is present in ~45–50% of patients with MM, and is commonly associated with non-HRD tumours[33,78–80]. This deletion is also present in patients with MGUS, suggesting a role as a primary event in early oncogenesis of the disease[22]. In approximately 85% of patients with del(13q), this deletion affects the whole q arm, whereas various interstitial deletions occur in the remaining 15%[78,81]. The prognostic value of chromosome 13 deletions, and the location of tumour suppressor genes (potential or confirmed) have been extensively investigated. The minimally deleted region lies between 13q14.11–13q14.3 and contains 68 genes, including *RB1*, *EBPL*, *RNASEH2B*, *RCBTB2*, and the microRNAs *mir-16-1* and *mir-15a*[55]. Molecular studies have shown that patients harbouring these deletions have considerably low levels of the tumour suppressor gene *RB1* than those without such deletions, which might result in reduced ability to negatively regulate the cell cycle[55]. Establishing the prognostic significance of del(13q) is challenging because this alteration is frequently associated with other high-risk cytogenetic lesions, such as t(4;14)[82]. Thus, the historical link[83] between del(13q) and a poor prognosis is a surrogate of its association with such lesions.

17p deletion. Most chromosome 17 deletions are hemizygous, affect the whole p arm and are observed in around 10% of patients with newly diagnosed MM, a frequency that increases up to 80% in the later stages of the disease[31,84]. This minimally deleted region includes the tumour suppressor gene *TP53*, and mutations in this gene are coexistant in 25–40% of patients harbouring del(17p)[9,85]. The *TP53* gene, which has been mapped to 17p13, functions as a transcriptional regulator influencing cell-cycle arrest, DNA repair, and apoptosis in response to DNA damage. In patients with MM, loss of 17p is associated with adverse overall survival outcomes and the development of extra-medullary disease[31,33,55,86,87].

Focal CNVs
New computational tools enable better sensitivity in the identification of focal CNVs[88–90], which helps to considerably narrow down the list of candidate driver genes affected by these changes. In addition to the focal changes located in regions of large CNVs discussed previously, other well-identified focal changes have been described[6,54] (FIG. 2). For example, gain of 8q24.21 is present in 14% of patients and involves *MYC*, a master regulator of MM. Gain of 11q13.2 is detected in about 15% of patients and this region contains *CCND1*, an oncogene with a central role in MM that is also affected by chromosomal translocations and somatic mutations. Deletion of 14q32.32 occurs in 10% of patients with MM and involves *TRAF3*, a gene implicated in the non-canonical NF-κB pathway[58]. *TRAF3* is also among the genes most frequently mutated in patients with MM (FIG. 3).

Single-nucleotide variants and indels
The intensive application of massively parallel sequencing has enabled the completion of several WES studies, generating a comprehensive compendium of driver genes across MM[5–7,9]. To date, three cohorts of patients with MM have been studied using WES[5–9]. The initial study[5,6] included 203 patients, with WES performed both at diagnosis and at relapse; samples from 23 of these patients were analysed using whole-genome sequencing[5,6]. Another cohort incorporated 67 patients at diagnosis or relapse, with sequential samples (from before treatment and at relapse) available for 15 patients[7]. The last published WES study comprised samples obtained at the time of diagnosis from 463 patients with MM enrolled in the National Cancer Research Institute Myeloma XI trial[8,9].

Median mutation rate in MM
When considering all cancer types analysed to date, the somatic mutation rate of patients with MM is at the median, with an average of 1.6 mutations per Mb — compared with <0.5 mutations per Mb in paediatric cancers, such as rhabdoid tumours or Ewing sarcoma, and ~10 mutations per Mb in patients with melanoma or lung cancer[91,92]. The importance of the cohort size is critical to infer driver genes, as demonstrated by downsampling analysis[92]; considering the mutation rate of patients with MM, for example, a cohort of 500 patients would provide a power of 99% to detect mutations

Combined WES in MM (% mutated cases)

Gene	Walker et al. % (n = 463)	Lohr et al. % (n = 203)	Boli et al. % (n = 67)
KRAS	21*	23*	20*
NRAS	19*	20*	20*
FAM46C	6*	11*	10*
BRAF	7*	6*	12*
TP53	3*	8*	12*
DIS3	9*	11*	1
PRDM1	–	5*	–
SP140	–	4	6*
EGR1	4*	4	6
TRAF3	4*	5*	2
ATM	3	4	3
CCND1	2*	3	4
HISTH1E	3*	–	–
LTB	3*	1	4*
IRF4	3*	2	–
FGFR3	3*	2	–
RB1	2	3*	–
ACTG1	–	2*	–
CYLD	2*	2*	1
MAX	2*	1	–
ATR	1	1	2

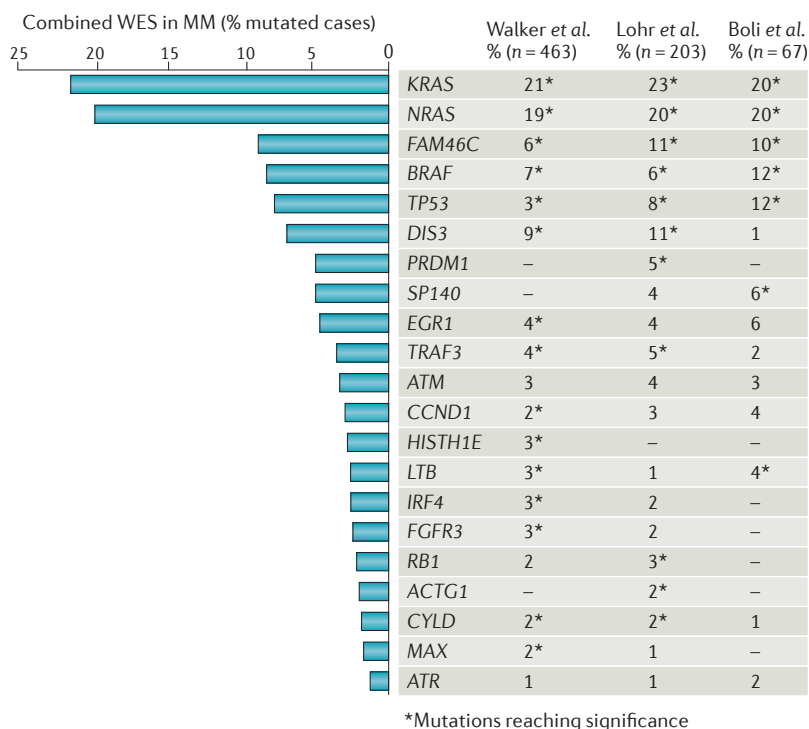*Mutations reaching significance

Figure 3 | **Most frequent somatic mutations in patients with multiple myeloma.** Mutation frequencies were calculated by averaging the data from three whole-exome sequencing studies comprising a total of 733 patients[6,7,9]. MM, multiple myeloma; WES, whole-exome sequencing.

proportion of patients evaluated in one of the three published WES studies[6,7,9] (FIG. 3). The clinical relevance of mutations in these genes has been evaluated in 463 patients enrolled in the Myeloma XI clinical trial[9].

Mutations affecting the MAPK pathway, including those in *KRAS*, *NRAS* and *BRAF* (FIG. 4), are the most frequently observed pathway mutations in MM, and are detected in ~40% of patients. These mutations are frequently subclonal, thus likely associated with disease progression[6,9]. The presence of mutations affecting the MAPK pathway is not associated with improved progression-free or overall survival[9].

Genes encoding components of the NF-κB pathway, such as *TRAF3*, *CYLD* and *LTB* (reaching statistical significance), and *IKBKB*, *BIRC2*, *BIRC3*, *CARD11* and *TRAF3IP1* (not statistically significant), are also recurrently mutated in MM (FIG. 4)[9,58]. Indeed, the NF-κB pathway is enriched in mutated genes in MM[6], which occur in ~20% of patients. Similarly to the MAPK pathway, the NF-κB pathway has no effect on the survival outcomes of newly diagnosed patients with MM[9].

Genes involved in the DNA-repair pathway (*TP53*, *ATM* and *ATR*) are mutated in about 15% of patients with MM (FIG. 4)[9]. The *ATM* and *ATR* kinases are recruited and activated by DNA double-strand breaks or DNA-replication stress, respectively[95]. Their activation induces the phosphorylation of p53, Chk1 and Chk2, thus leading to cell-cycle arrest, DNA repair or apoptosis. Mutations in these genes are associated with an unfavourable outcome in patients with MM[9].

DIS3 and *FAM46C* are two of the most recurrently mutated genes in MM. These genes are both considered potential tumour suppressor genes, but their role in MM oncogenesis is unclear. *DIS3*, also known as *RRP44*, encodes a highly conserved RNA exonuclease, which is part of the exosome complex involved in regulating the processing and abundance of RNA[96,97], and participates in the elimination of unstable mRNA and processing of stable snoRNA, tRNA or rRNA[94,95]. Mutations in *DIS3*, postulated to be loss-of-function mutations, cluster in the region encoding the enzyme's catalytic pocket (RNase II/R domain)[98]. *FAM46C* is less well-characterized, but is considered a tumour suppressor gene that is functionally related to the regulation of translation[5].

Other genes significantly mutated in MM, such as *PRDM1*, *IRF4*, *LTB* and *SP140*, are involved in B-cell lineage differentiation (FIG. 4). *PRDM1* (also called *BLIMP1*) encodes a transcriptional repressor essential for plasma-cell differentiation. Loss-of-function mutations of *PRDM1* have been detected in patients with diffuse large B-cell lymphoma[99,100]. In MM, the mutational profile of *PRDM1* (truncated frameshift and splice-site mutations) also suggests a tumour repressor role[6]. *IRF4* encodes a transcriptional regulator of *PRDM1*, and is also recurrently mutated in MM. Together with *PRDM1*, *IRF4* represents a key regulator of B-cell differentiation. In patients with MM, mutations in *IRF4* preferentially affect a hotspot at K123R within the interferon regulatory factor domain. Oncogenic *IRF4* mutations are associated with a favourable prognosis for newly diagnosed patients with MM[9].

present in ≥5% of patients, and a power of 72%, 28% and 2% to detect mutations present in 3%, 2% and 1% of the patients, respectively. Therefore, cohorts of >500 patients will be required to identify the presence of rare driver mutations, that is, those affecting <1% of patients in MM.

Mutational signatures in MM

Across human cancer types, 21 mutational signatures have been described[93]. Some of them are associated with the age of the patient at diagnosis, known exposure to mutagens (such as smoking or ultraviolet light), or defects in DNA mismatch repair, whereas the origin of many others is unknown. The mutations associated with MM can be grouped within two different mutational signatures[7,8,93]: a generic signature that predominantly comprises C>T mutations in regions rich in 5-methyl-CpG; or the APOBEC signature, that consists of C>T and C>G mutations in TCN trinucleotide repeats, in which the cytosine nucleotides are methylated. This signature is one of the most frequent mutational signatures across all cancer types[93] and has been postulated to result from the overactivation of members of the APOBEC family of cytidine deaminases[94], which convert cytidine to uracil. As discussed previously, this signature is enriched in patients with MM harbouring t(14;16) and t(14;20)[8].

Pathways affected by driver mutations

Several genes are recurrently mutated and, therefore, considered to be driver events in MM oncogenesis. Of these genes, 16 were found to be mutated in a significant
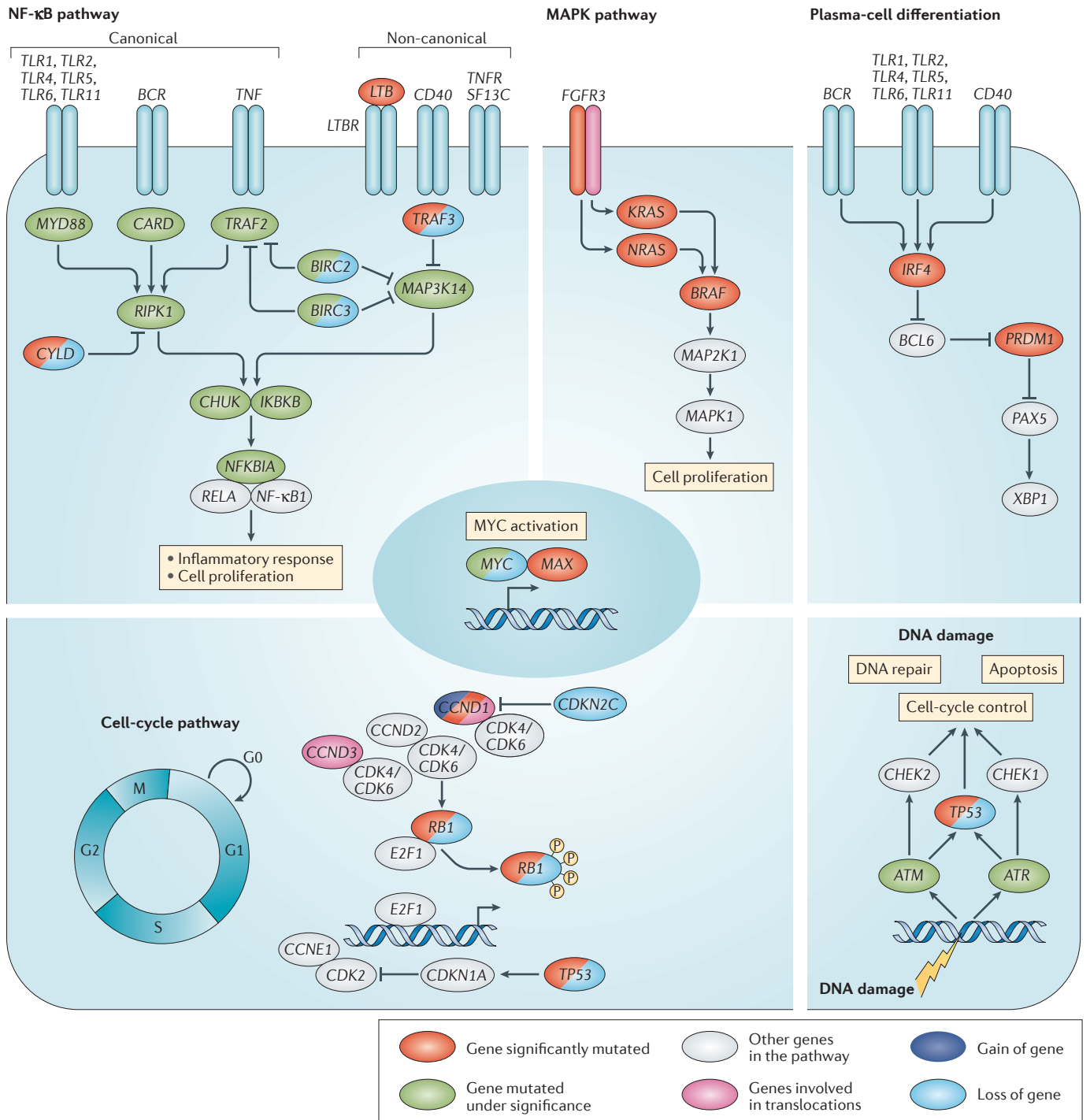
Figure 4 | Recurrent genetic alterations affecting key pathways involved in multiple myeloma. Signalling pathways and processes known to be affected in multiple myeloma are involved in the NF-κB, MAPK, plasma-cell differentiation, cell cycle and DNA-damage repair pathways. In this diagram, frequently mutated genes with well-established roles in these signalling pathways have been depicted representing the proteins they encode.

Clonal heterogeneity and evolution

The ability of cancer cells to evolve and adapt is caused by the coexistence of multiple and genetically hetero-geneous subclones within the tumour cell population (BOX 1). Increasing evidence has supported the idea of a Darwinian selection process, by which the genomic landscape of the tumour is shaped by the differential fitness of subclones[101–103].

Clonal heterogeneity can be assessed in WES data by analytic deconvolution of clonal complexity within each sample and subsequent calculation of the proportion of cancer cells in which each mutation is present[104,105].

Box 1 | Darwinian evolution in cancer

Clonal evolution is the process whereby cell populations are selected on the basis of a fitness advantage gained from somatic mutations that either increase cell proliferation or decrease the rate of cell death[121]. Clonal evolution in cancer mirrors Darwinian evolution, a process in which each genetic change confers a growth advantage to the cell or organism[122]. In cancer, clonal evolution occurs in the context of selection events induced by selective pressures present in the tumour microenvironment, such as immune surveillance, clonal competition or drug treatment. The clonal evolution model gives rise to the concept of driver mutations (those providing fitness advantage) as opposed to passenger mutations (those with a neutral effect). According to Darwinian evolution, driver mutations will be selected based on the fitness advantage they provide to cells or organisms. The quest to understand such mutations in cancer will provide insight into novel approaches to manage disease progression, such as enhancing the host antitumour immune response or avoiding resistance to therapy, among others.

Mutations are defined as clonal when they are harboured by all cancer cells and subclonal when they occur in a subpopulation of cancer cells. Results of WES show that patients with MM harbour, on average, five detectable subclones — with some patients having as many as ten — thus reaffirming that MM tumours are highly heterogeneous. These results are an underestimate of the true clonal heterogeneity in MM because the sensitivity of the current techniques enables only the detection of subclones representing at least 10% of the entire tumour sample[6]. Most of the genes recurrently mutated in MM are found to be clonal in some patients and subclonal in others[6,7] (FIG. 5). Other mutated genes (such as *MAX*, *RB1*, *CCND1* or *TP53*) are more frequently clonal than subclonal, suggesting they represent early events in disease progression, or are capable of enforcing a 'selective sweep' during therapy. Finally, some genes are more frequently subclonal (such as *FAM46C* or *TRAF3*), and likely represent late events in disease progression[6]. In a cohort of 203 patients with MM[6], mutations in *KRAS*, *NRAS* and *BRAF* were clonal in about 70% of the patients and subclonal in the remaining 30%. However, this study included a mixture of patients analysed at diagnosis and at relapse; thus, it might be difficult to distinguish patterns of clonal evolution that occurred as part of the natural history of the disease from those that resulted from the strong selection pressures applied by effective therapy[6]. In fact, the genes recurrently mutated were more often clonal in previously treated patients and subclonal in newly diagnosed patients, suggesting a selection of the fitter clones by therapy[6]. Further studies of the clonal heterogeneity at pre-malignant, newly diagnosed, and relapsed stages need to be performed to better distinguish early from late genomic events in MM.

Co-occurrence of genomic events

Mutations in *KRAS* and *NRAS* do not usually arise together[6,106]. When these mutations do coexist in the same tumour, they almost always occur at a subclonal level and not simultaneously at a clonal level[62]. This mutual exclusivity was further confirmed in a study in which samples derived from patients with MM were analysed at the single-cell level[104]. The results of this study indicated that the mutations affecting the MAPK pathway had occurred more than once within the same tumour, but in distinct subclones evolving separately[106].

Studying the co-occurrence of genomic events enables recurrent combination patterns of mutations or structural variants to be defined, thus providing new insight into the pathogenesis of MM (FIG. 6). HRD and translocations affecting *IGH* are mutually exclusive in a large majority of patients[9,63,107], although these chromosomal aberrations can coexist in a small fraction (~7%) of patients[64]. HRD is correlated with mutations in *NRAS*, and, to a minor extent with translocations involving *MYC* and mutations in *EGR1*[9]. The t(11;14) translocation is associated with mutations in *KRAS*, *IRF4* and *CCND1*, whereas t(4;14) co-segregates with mutations in *FGFR3*, *DIS3* and *PRKD2*, or with del(12p), del(13q) and gain of 1q[9]. Translocation t(14;16) shows a similar association pattern as t(4;14), including mutations in *DIS3*, del(13q) and gain of 1q, but also co-segregates with mutations in *MAF* and *PRDM1*[9].

Dynamics of clonal evolution

Clonal evolution reflects modifications in clonal heterogeneity over time — for example, from pre-malignant stages to overt MM, or from pretreatment to posttreatment conditions for patients with MM. These patterns can be studied by sequencing of sequential samples (at a minimum of at least two time points) from the same patient, or by single-cell sequencing of a sample at a single time point, in order to infer the phylogeny of the tumour[101].

Although MGUS and SMM are less genetically complex than MM, clonal heterogeneity is already present at these early pre-malignant stages, as determined by the results of WES sequencing analysis of paired highrisk SMM and MM samples from four patients, which revealed that all the predominant subclones at the MM stage were already present at the SMM stage[108].

Clonal evolution in MM before and after therapy can follow several patterns: a linear clonal shift, a branching
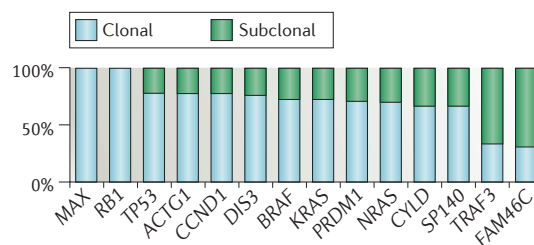
Figure 5 | Clonal heterogeneity in multiple myeloma. For the most frequently mutated genes in multiple myeloma, the percentage of patients in whom the mutations were classified as clonal or subclonal are represented in blue or green, respectively. Data depicted were generated from the results of a whole-exome sequencing study in 203 patients[6].
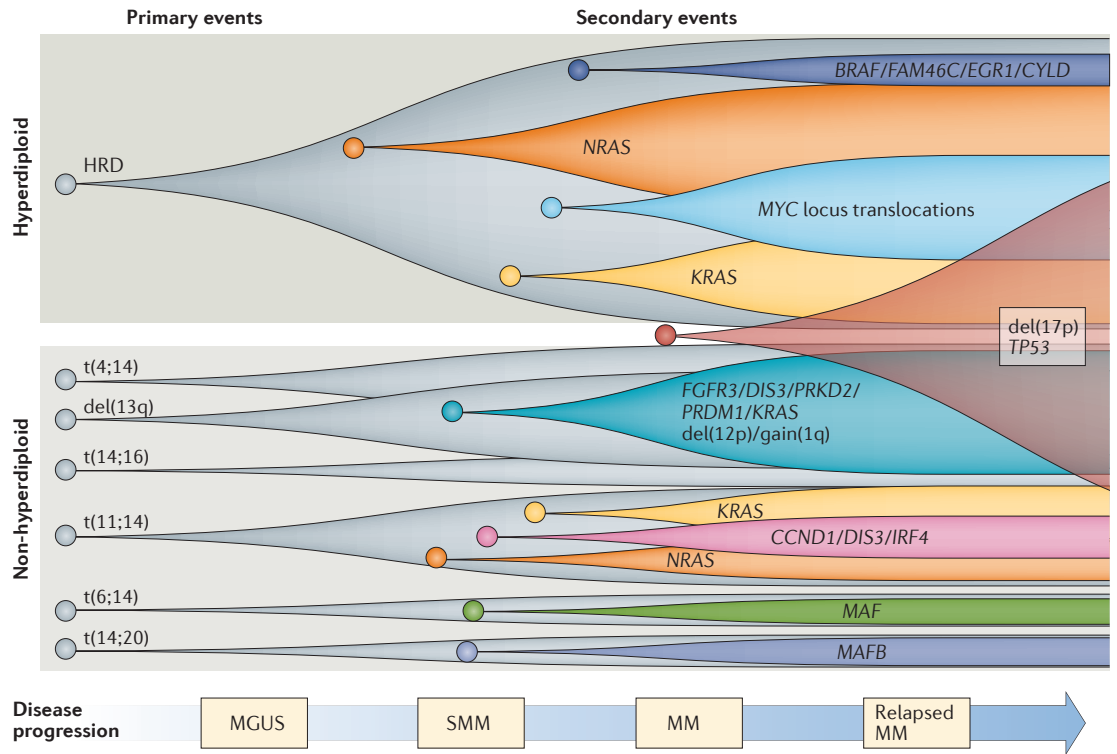
Figure 6 | **Proposed model of clonal evolution in multiple myeloma.** This model represents the most frequently co-occurring mutations that drive clonal evolution from monoclonal gammaopathy of undetermined significance (MGUS) to multiple myeloma (MM). Clones are represented as circles. The primary genomic events affecting certain clones (represented in grey) include hyperdiploid tumours (HRD), translocations in the genes encoding the immunoglobulin heavy chains (*IGH*), and 13q deletion. Secondary events (coloured clones) are represented on the background of the main primary events with which they are associated[6,9]. Translocations involving *MYC* can still be detected in some individuals harbouring translocations affecting *IGH*, but have not been depicted for clarity. Moreover, del(17p) can arise in any multiple myeloma clones, and has been represented at the intersection of HRD tumours and non-HRD tumours. del, deletion; SMM, smouldering multiple myeloma; t, translocation.

clonal shift or stability of the tumour, with no changes in subclonal heterogeneity[7,106]. In the case of linear evolution (which occurs in ~40% of patients), a shift in the subclonal population distribution can be observed, indicating that either a new subclone emerges or a pre-existing subclone becomes predominant at the later time point, resulting in an apparent stepwise acquisition of driver mutations. Branching clonal evolution (observed in ~25% of patients) involves one or more subclones emerging at the later time point — through divergent mutational pathways — while other subclones decline in frequency or disappear. Finally, in situations of clonal stability (occurring in 35% of patients with MM), the same composition of clonal and subclonal heterogeneity is found before and after treatment, suggesting that all subclones are affected by therapy and will repopulate the tumour equivalently. Of note, the complexity of subclonal heterogeneity is dependent on the sensitivity of the assay, especially the depth of sequencing, used to evaluate such heterogeneity. In addition, the indicated percentages were observed in a cohort of only 15 patients from whom sequential samples were obtained[7]; ideally, larger cohorts are needed to better characterize the clonal evolution patterns of MM.

Clinical impact

One of the key areas in progress in the genomic characterization of MM is the critical need to comprehensively implement precision medicine. To this end, efforts have been made to annotate specific genetic lesions with matching prognostic or predictive information (TABLE 2).

Prognostic markers

Genomic lesions were found to have relevant prognostic value in a study comprising 463 patients enrolled in the Myeloma XI clinical trial[9]. A new prognostic model was developed by combining the International Staging System (ISS), a risk stratification algorithm based on measuring the levels of two proteins in serum (β-2-microglobulin and albumin)[109], with information on several genomic events, including mutations affecting *TP53, ATM or ATR, ZFH4* or *CCND1,* del(17p), t(4;14), amp(1q), and translocations involving *MYC*. The model developed in this study[9] had enhanced sensitivity in the early detection of disease progression and early prediction of mortality risk in patients with MM, as compared with the ISS, although the data need further validation in other independent cohorts. At present, the ISS[109] and the updated revised-ISS[87], which combines FISH

analysis of t(4;14) and del(17p), serum levels of lactate dehydrogenase and the ISS, remain the 'gold standard' staging systems.

Actionable mutations

Perhaps more importantly, precision medicine aims to tailor the appropriate therapy to each patient in a personalized fashion, on the basis of the genomic information available for that disease. To this end, the identification of driver mutations in MM holds great promise for the implementation of precision medicine, whereby patients with particular mutations would be treated with the appropriate targeted therapy (TABLE 3). A report published in 2013 describes a durable response (>7 months at the time of reporting) of a patient harbouring the activating mutation of *BRAF* V600E to the mutation-specific BRAF inhibitor vemurafenib[110]. Among the genes recurrently mutated in patients with MM, several are potentially 'actionable' (that is, they can be targeted by therapies specifically inhibiting the mutated or activated oncogene; TABLE 3). Nevertheless, the targeted therapy approach has to be considered in light of the clonal heterogeneity and clonal competitions co-occurring in the cancer cell population. In fact, *BRAF* inhibitors are known to paradoxically activate the MAPK pathway in the event of coexistent subclones harbouring mutated *KRAS* or *NRAS*, or wild-type *BRAF*[6,111]. This signalling interaction can be abrogated by combining inhibitors of BRAF and MEK[62]. Clonal heterogeneity poses a substantial challenge to the implementation of precision medicine; indeed, most relapsed cancers show marked differences in their genetic makeup compared with pretreatment tumours. This variability raises the issue of determining the most effective therapeutic combinations. Thus, the comprehensive understanding of clonal heterogeneity is crucial to further develop targeted therapies for MM.

Immunotherapy provides an alternative approach that might help to overcome these challenges; however, the potential effects of new immunotherapeutic

Table 2 | **Main genomic alterations in multiple myeloma and their clinical impact**

Genomic event	(Potential) driver genes involved	Frequency in patients with MM	Prognostic value
Primary events			
Translocations: driver genes	t(11;14): *CCND1* (REFS 8,29,31)	15%	Neutral or adverse*
	t(4;14): *FGFR3/MMSET*[27–31]	15%	Adverse
	t(6;14): *CCND3* (REF. 45)	2%	Neutral
	t(14;16): *MAF*[29,42,46]	5%	Neutral or adverse‡
	t(14;20): *MAFB*[46]	1%	Adverse
Copy-number variations	Hyperdiploidy: tri 3, 5, 7, 9, 11, 15, 19 or 21 (REFS 64,65)	50%	Favourable
	del13q: *RB1, DIS3, mir15a* or *mir16.1* (REFS 53,69) (potential drivers)	40%	Neutral§
Secondary events			
Chromosome gains: potential driver genes	1q: *MCL1, CKS1B, ANP32E* or *BCL9* (REFS 9,66,70)	40%	Adverse
	8q: *MYC*[8]	15%	Neutral
	11q: *CCND1* (REF. 77)	15%	Neutral
Chromosome losses: potential tumour suppressor genes	1p: *CDKN2C* or *FAM46C*[53,75,77]	30%	Adverse
	12p: *CD27* (REF. 77)	15%	Adverse
	14q: *TRAF3* (REF. 53)	10%	Not determined
	16q: *CYLD* or *WWOX*	30%	Neutral
	17p: *TP53* (REF. 85)	10%	Adverse
Translocations	Affecting *MYC*[8,9]	15%	Adverse
Somatic mutations[9]	MAPK pathway: *KRAS, NRAS* or *BRAF*	45%	Neutral
	NF-κB pathway: *CYLD, TRAF3, LBT* or *NIK*	15%	Neutral
	RNA metabolism: *DIS3* or *FAM46C*	15%	Neutral
	DNA-repair pathway: *TP53, ATM* or *ATR*	10%	Adverse
	Plasma cell differentiation: *IRF4* or *PRDM1*	10%	Favourable

del, deletion; MM, multiple myeloma; t, translocation; tri, trisomy. *The prognostic value of t(11;14) is considered neutral, but this translocation is associated with poor prognosis when it co-occurs with *CCND1* mutation. ‡t(14;16) has been defined to have both adverse[31] and neutral[44] effects on prognosis. §del13q has been traditionally associated with a poor prognosis, which is now believed to be a surrogate of its association with other high-risk lesions[82].

Table 3 | **Actionable mutations in multiple myeloma**

Alteration	Frequency	Targeted therapy	Drug development in oncology (clinical trial ref. number)
Mutations in *KRAS*	21%[6]	Selumetinib[123,124]	• Phase II in MM (NCT01085214) • Phase III (NCT01933932)
Mutations in *NRAS*	20%[6]	Cobimetinib[125]	• Phase III (NCT01689519)
Translocations involving *MYC*	18%[8]	BET inhibitors[126]	• Phase I in MM (NCT02157636)
Mutations in *FGFR3*, t(4;14)	13%[8]	• BGJ398 (REF. 127) • AZD4547 (REF. 128)	• Phase II (NCT02160041) • Phase III (NCT02154490)
Mutations in *BRAF*	8%[6]	Vemurafenib[129]	• Phase II in MM (NCT01524978) • Phase III (NCT01689519)
del(1p) resulting in loss of *CDKN2C*	30%[6]	Palbociclib[130]	• Phase II in MM (NCT00555906 • Phase III (NCT01942135)
t(11;14) resulting in *CCND1* overexpression and mutations	19%[8]	Palbociclib[130]	• Phase II in MM (NCT00555906) • Phase III (NCT01942135)
t(6;14) resulting in *CCND3* overexpression	1%[8]	Palbociclib[130]	• Phase II in MM (NCT00555906) • Phase III (NCT01942135)

BET, bromodomain and extra-terminal motif protein; del, deletion; t, translocation.

approaches in MM, in the context of clonal heterogeneity, is currently unknown. Specifically, whether treatments such as the anti-CD319 antibody elotuzumab[112,113], the anti-CD38 antibodies daratumumab[114,115], chimeric antigen receptor (CAR) T cells (directed against B-cell maturation antigen (BCMA))[116] or the immunoglobulin κ light chain)[117]) or immune-checkpoint inhibitors (nivolumab[118] and atezolizumab[119]), will be effective regardless of the genomic characteristics of the tumour, and the effect of these strategies on clonal selection remains to be explored. Another potential therapeutic application of the characterization of the mutational landscape in MM is the development of novel vaccines and immune-checkpoint inhibitors. The immune response can now be dissected, and patient-specific neoantigens that arise from tumour-specific mutations can be identified[120] and, therefore, vaccines directed against these specific neoantigens could be administered in combination with immune-checkpoint inhibitors.

Conclusions

MM is a genetically complex and heterogeneous disease, in which a combination of primary events, secondary events and marked clonal heterogeneity lead to tumour development and progression from MGUS to late-stage MM. Most likely, several driver events need to coincide for the development and progression of the disease. The existence of clonal heterogeneity adds a layer of complexity by means of clonal competition during disease progression as well as in the context of therapeutic bottlenecks[101]. This genomic complexity is a challenge to finding effective therapies for patients with MM. The use of targeted therapies needs to take into account the context of clonal heterogeneity in patients with MM. In addition, the rapidly expanding characterization of somatic mutations in MM could lead to the identification of specific neoantigens that will enable the development of new therapeutic approaches by redirecting the immune system to target specific tumour clones. In this context, defining the role of the bone marrow microenvironment in modulating clonal evolution in MM will be critical for a better understanding of the mechanisms of disease progression and drug resistance[1].

Another layer of complexity in the genomic landscape of MM is arising from the study of noncoding mutations by whole-genome sequencing. Further studies will need to be performed on sequential samples taken before and after treatment to extend our knowledge of clonal evolution and to pinpoint resistant clones. Moreover, a better characterization of the genomic aberrations present in pre-malignant stages (MGUS and SMM) could help clarify the mechanisms that lead to tumour progression. Indeed, by identifying patients with a high risk of disease progression and developing early interventions using precision medicine, MM might become a curable or preventable disease.

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ERRATUM

Genomic complexity of multiple myeloma and its clinical implications

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In Figure 4, in the MYC activation subpanel, the genes depicted should be *MYC* and *MAX* instead of *BIRC2* and *NRAS*. This error has been corrected in the print and online versions of the article.