The genetic progression of Myeloma

Stéphane Minvielle, PhD

I have no conflicts of interest

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Multiple Myeloma

- Heterogeneous disease with some patients dying within a few weeks of diagnosis, while others live for longer than 10 years
- Nearly all patients relapse

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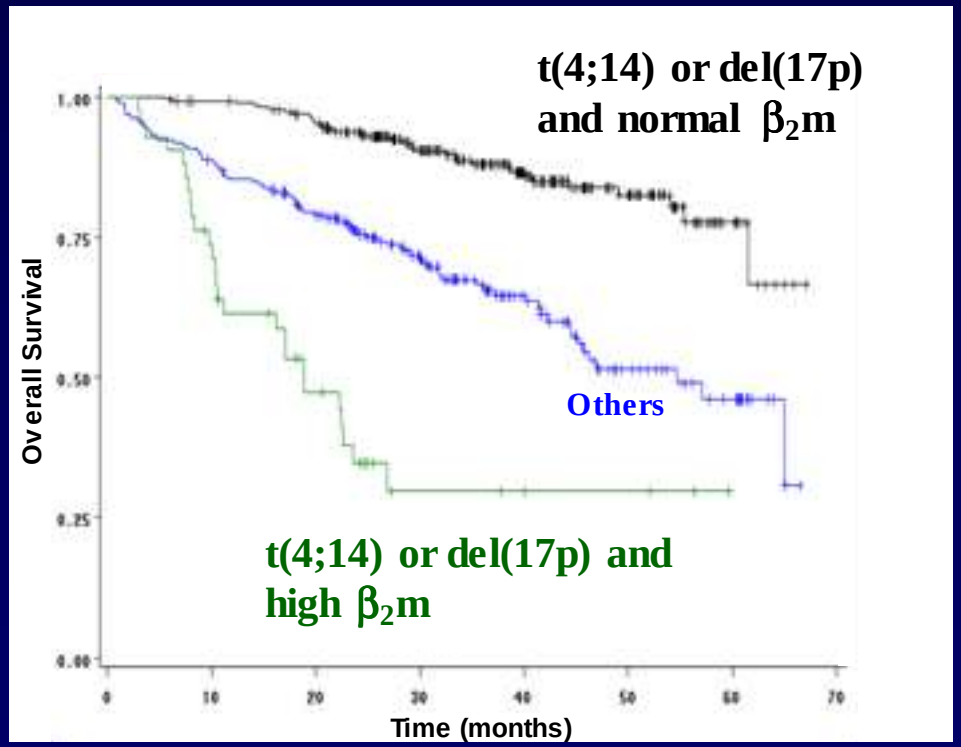

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- Nearly all patients relapse
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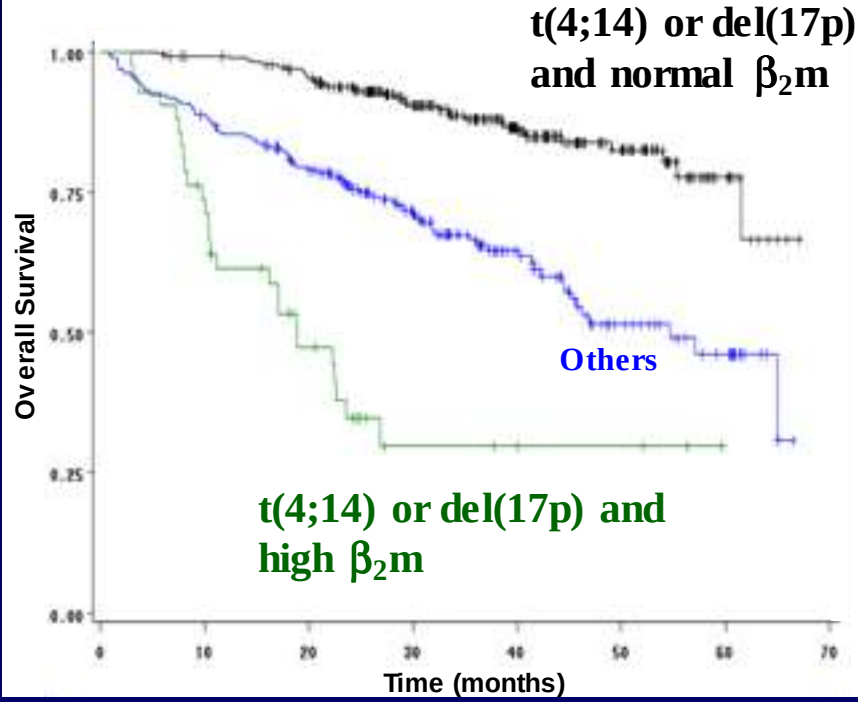
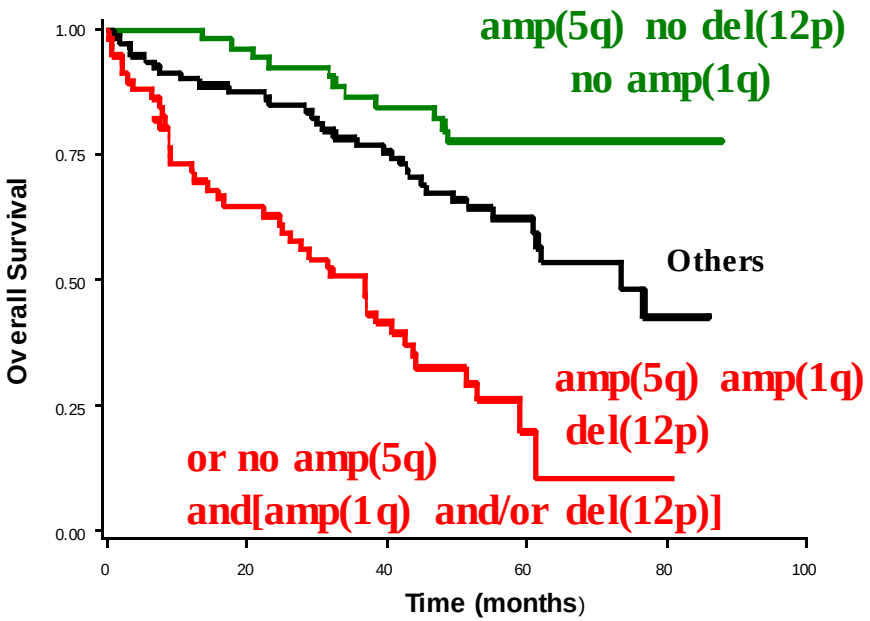
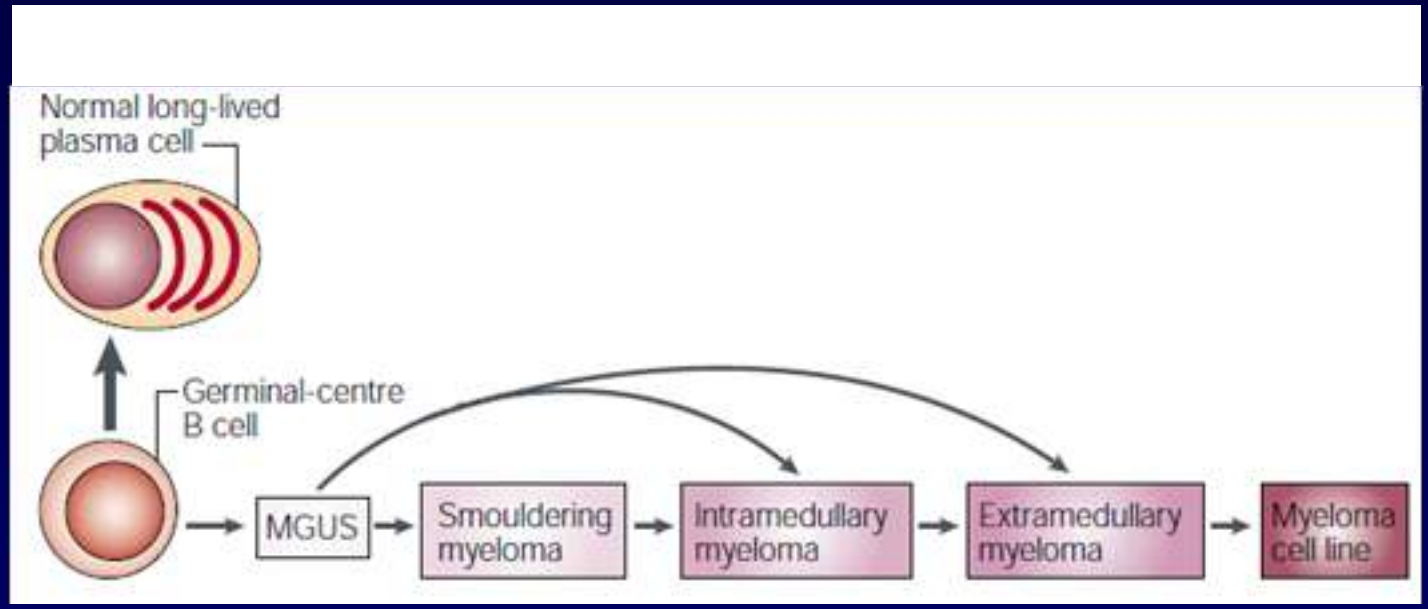




Gradual evolution

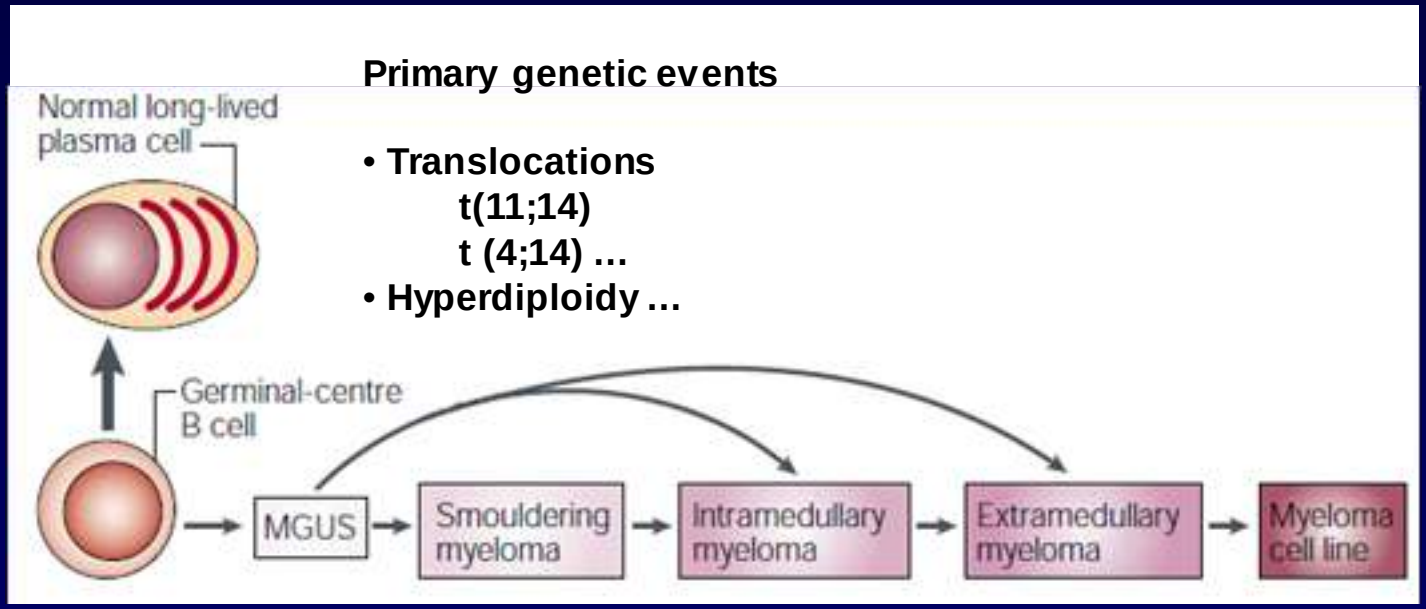
- **Multiple myeloma development model**



Adapted from Kuehl et al *Nature Review Cancer* 2002;2,175

Gradual evolution

- Multiple myeloma development model
- Multi-step process accumulating sequential genetic changes



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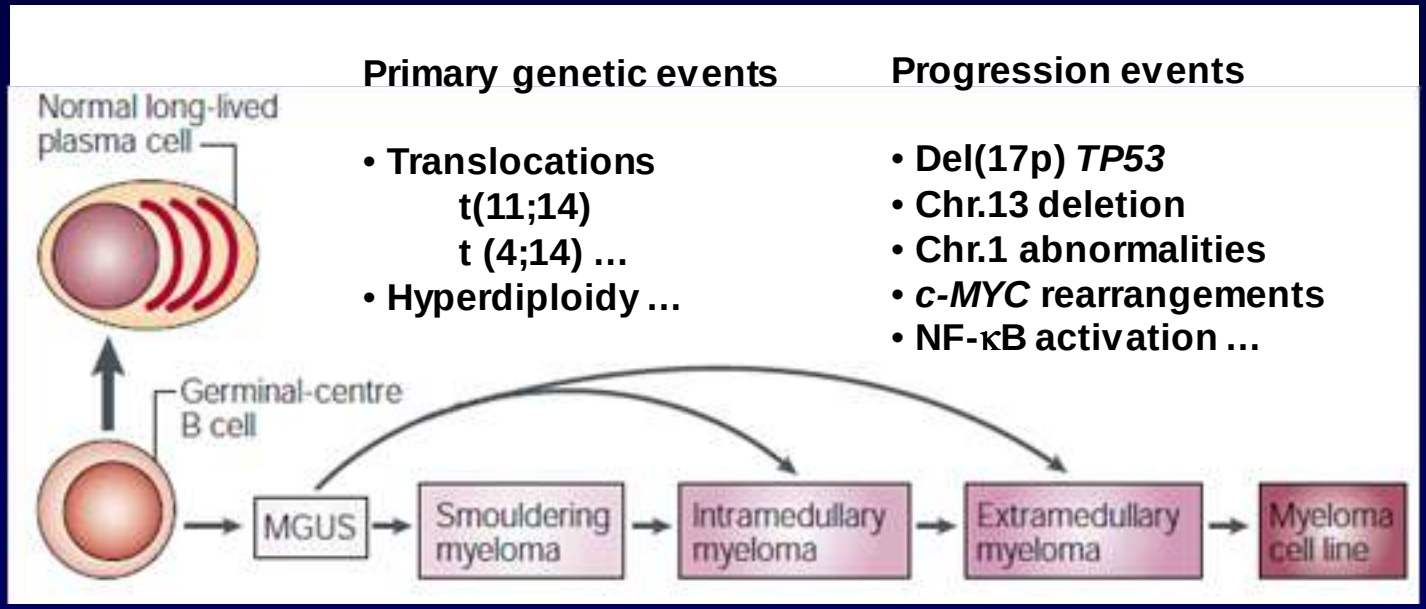

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How to study genetic progression ?

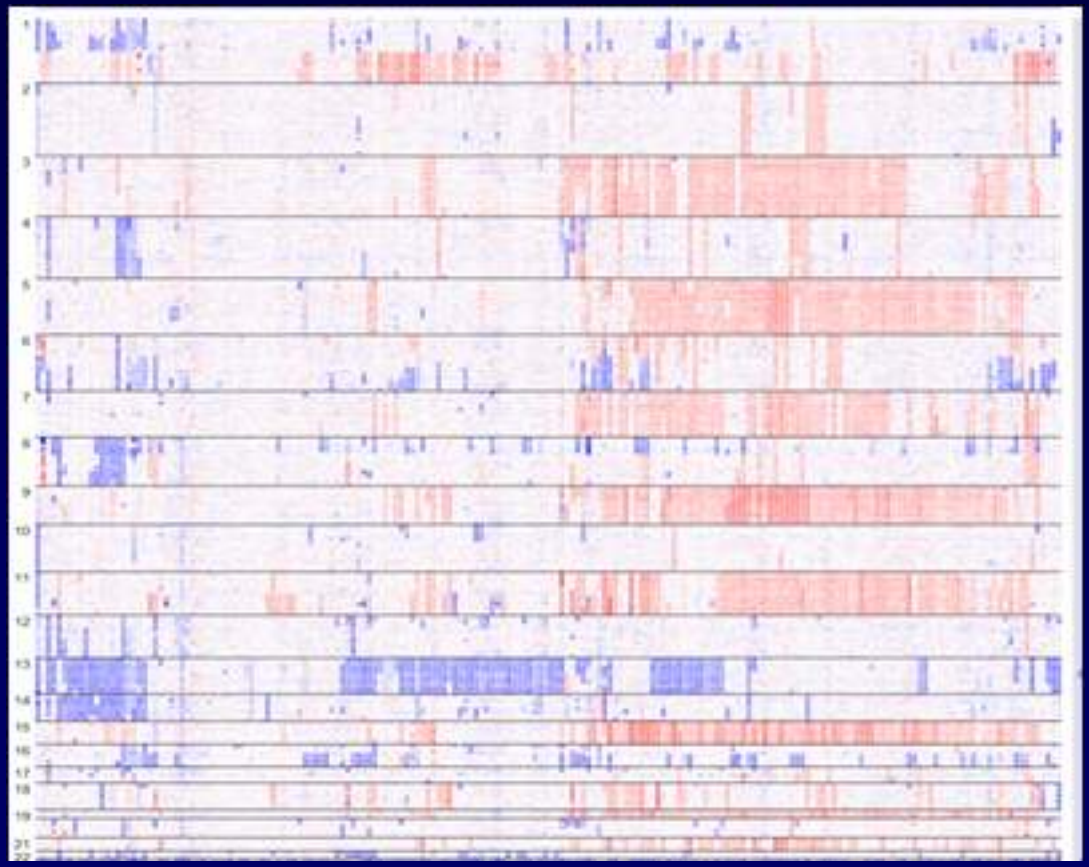
- Ideally: matched MGUS, SMM, MM, relapse samples in many patients
- In practice, paired diagnostic and relapse samples in a small cohort of patients
- Available tools
  - ✓ Targeted abnormalities (FISH)
  - ✓ Genome-wide allele specific copy number (SNP array)
  - ✓ Genome-wide intra /inter-chromosome rearrangements and point mutations (Whole-genome sequencing)

Genomic analyis from SNP array data

- CN and SNP markers (1.8 milions, intermaker distance < 1kb)
- Genome-wide copy number changes
- Landscape of genomic abnormalities

192 newly diagnosed patients

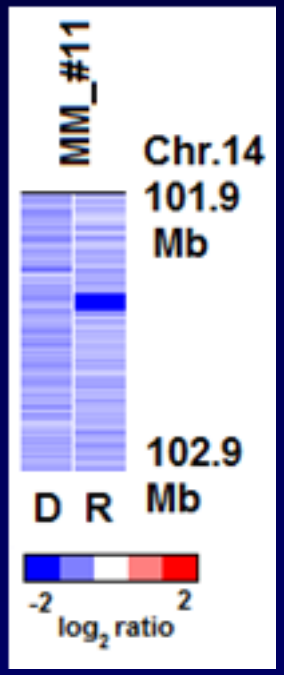
Chromosomes

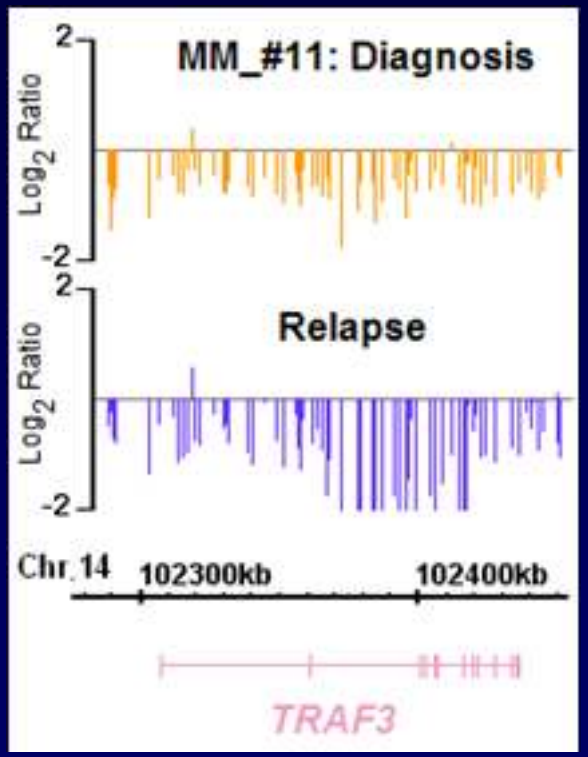


Avet-Loiseau et al, JCO 2009

Genomic analysis from SNP array data

- Identification of focal lesions (~ 50kb)

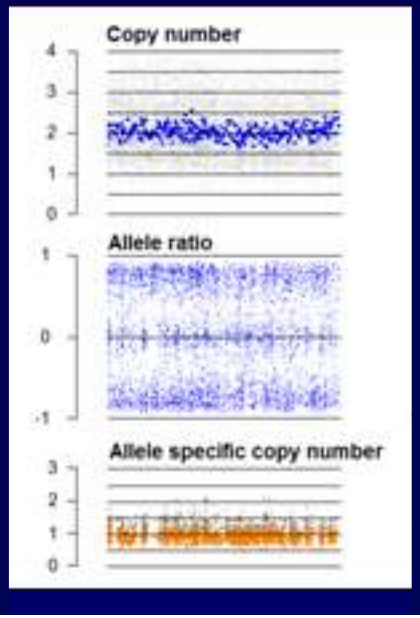




Genomic analysis from SNP array data

- Allelic copy number changes and allelic imbalance (0.9M SNPS)
  - Loss of heterozygosity (LOH)
  - Subpopulations identification

Normal diploid status



Genomic analysis from SNP array data

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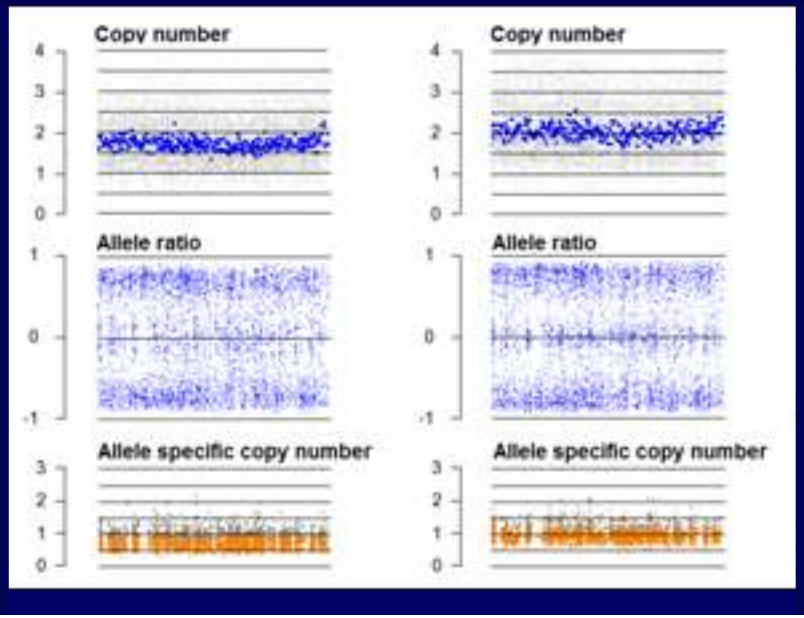
Deletion

Normal diploid status

40%



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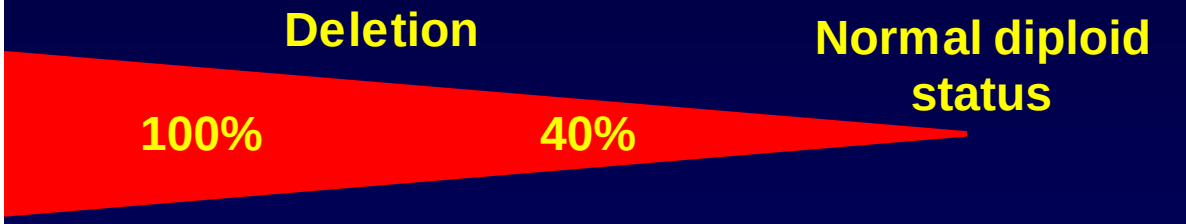

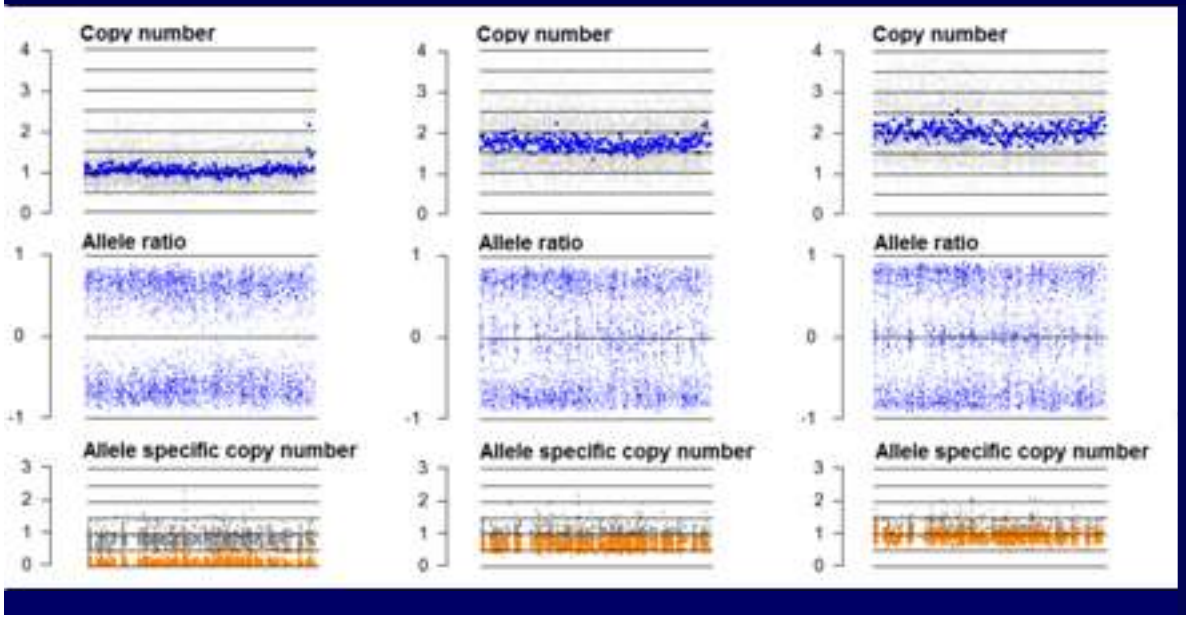

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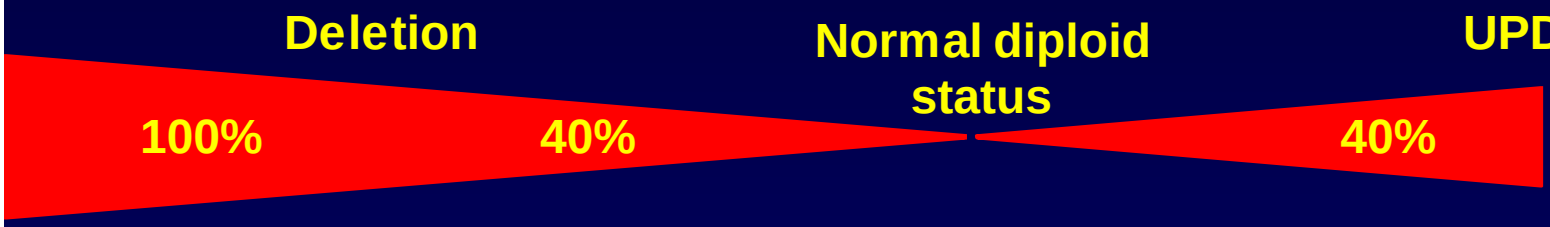

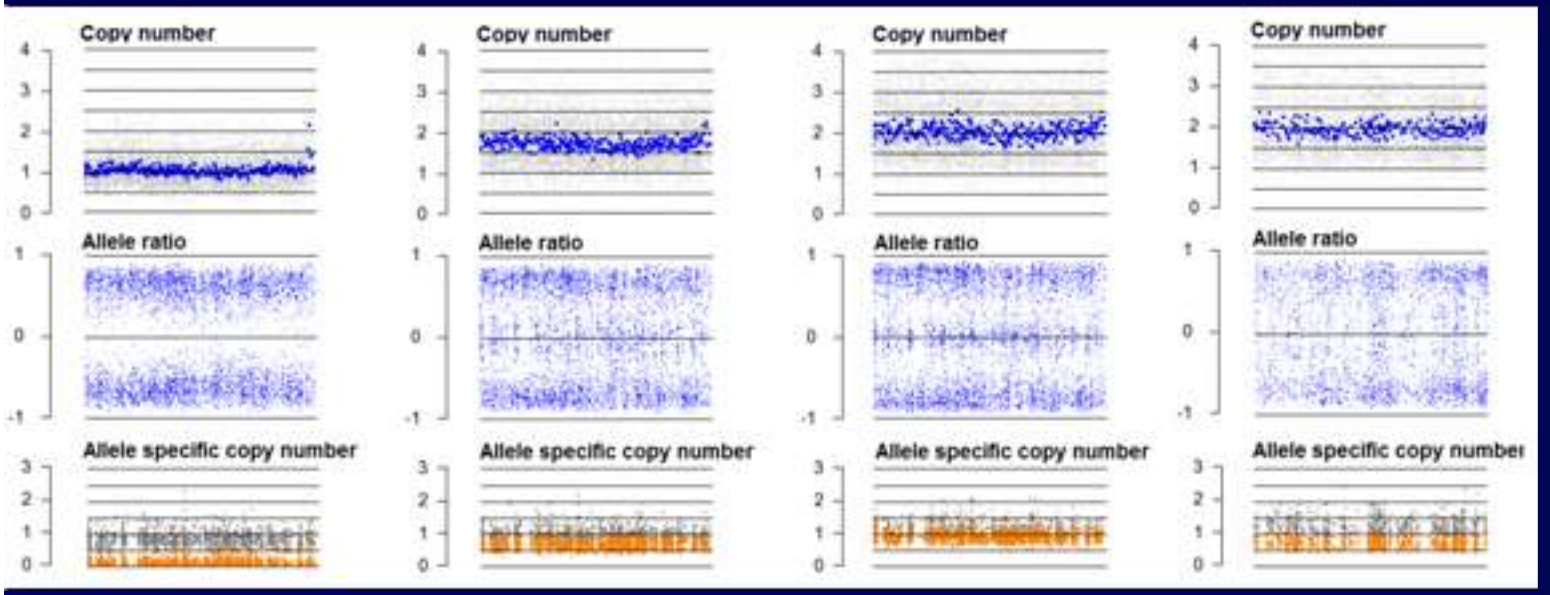

Genomic analysis from SNP array data

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Deletion

100%

40%

Normal diploid status

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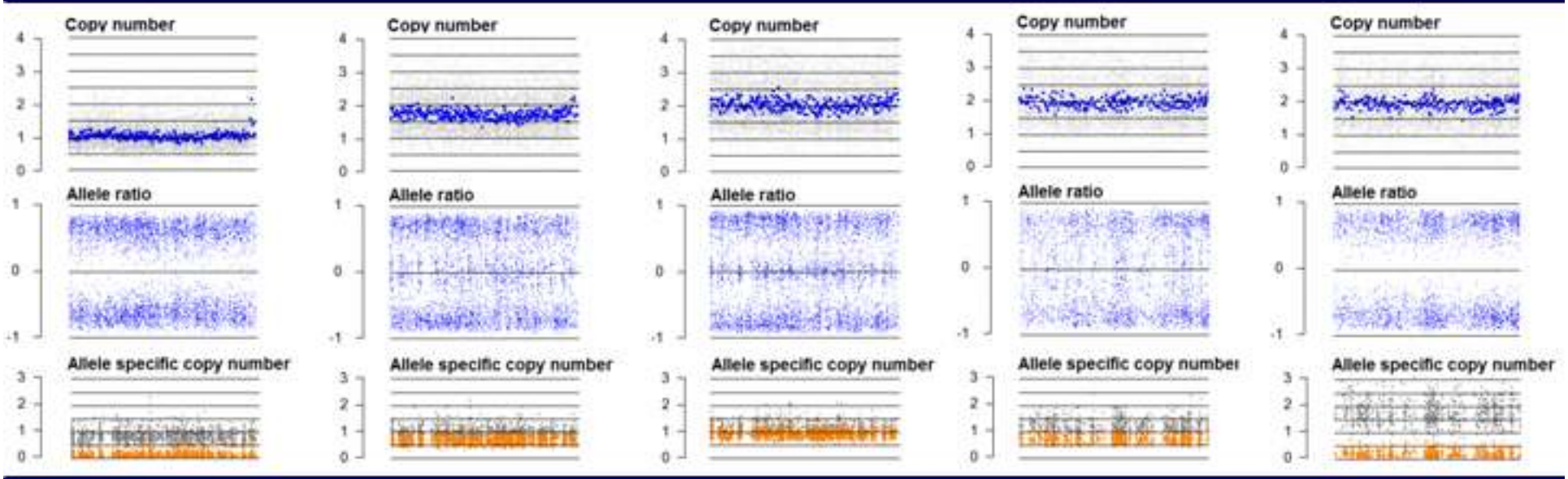
UPD/ CN-LOH

100%



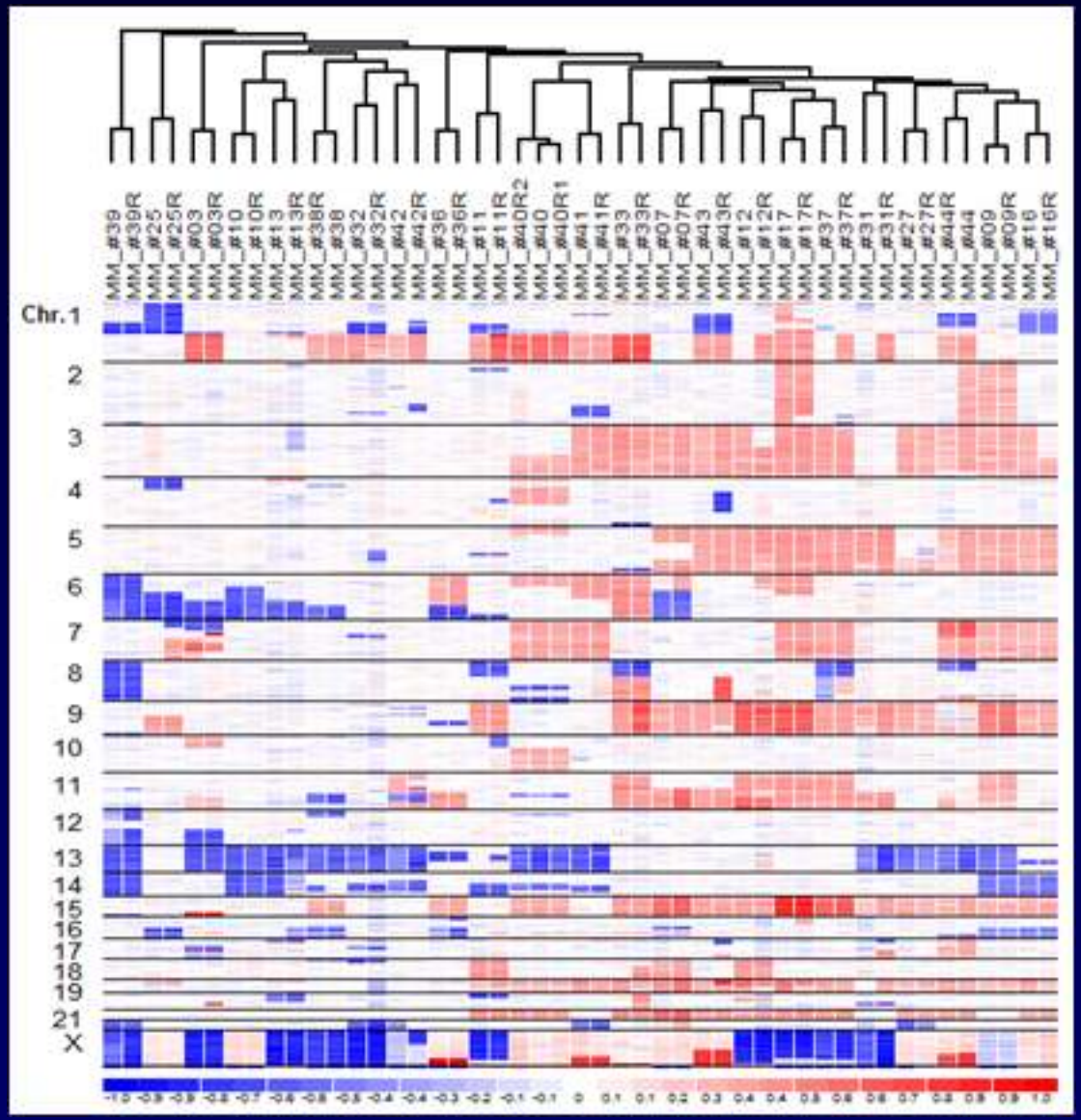
Analysis using genome-wide SNP arrays

MM Patients

- 24 patients; median age 59 years
- Matched diagnostic and relapse samples
- Induction treatment
  - VAD (n=12)
  - Bortezomib dex (n=12)
- Median follow-up (25 months)

Magrangeas et al, submitted

Analysis using genome-wide SNP arrays



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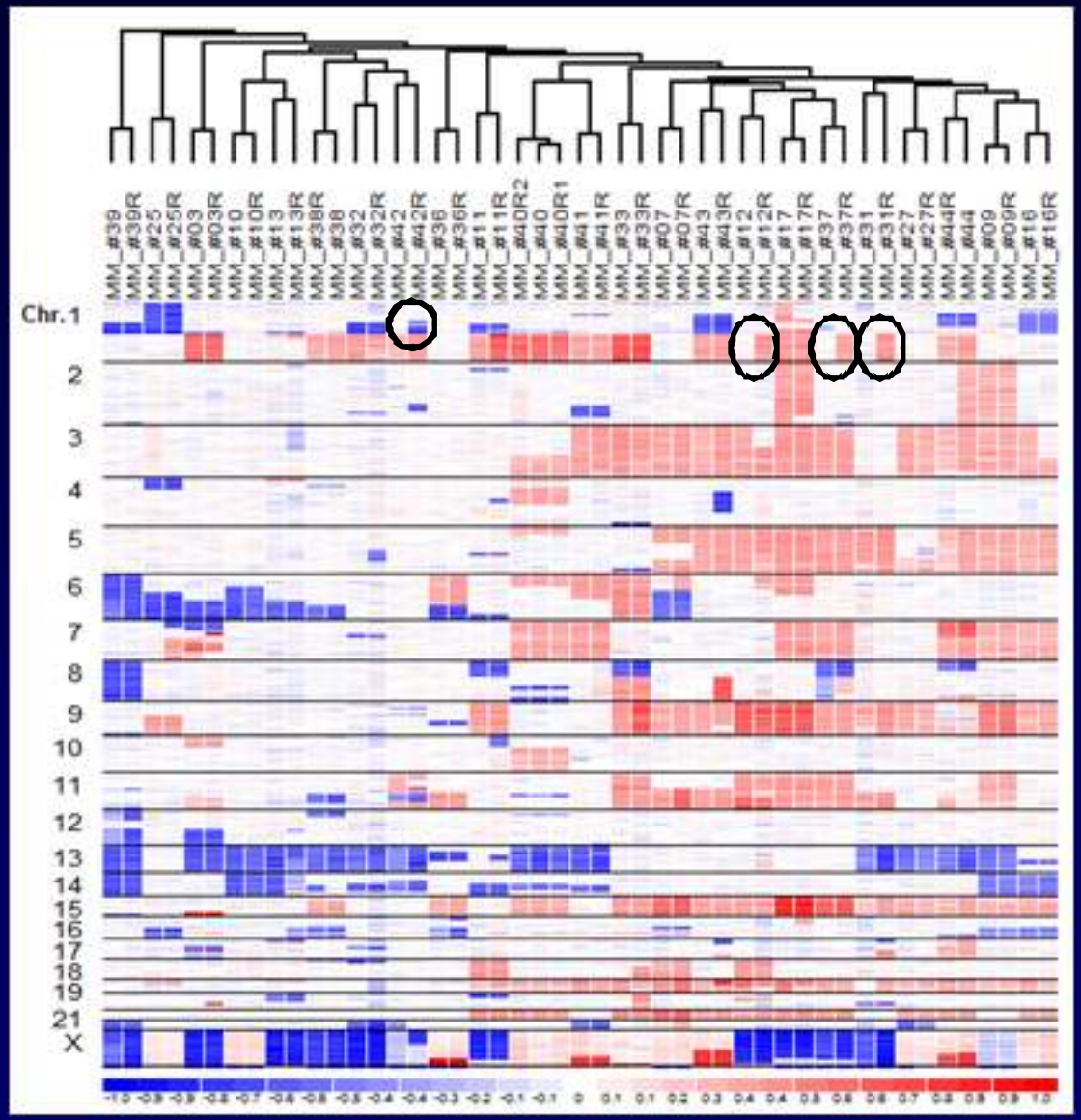

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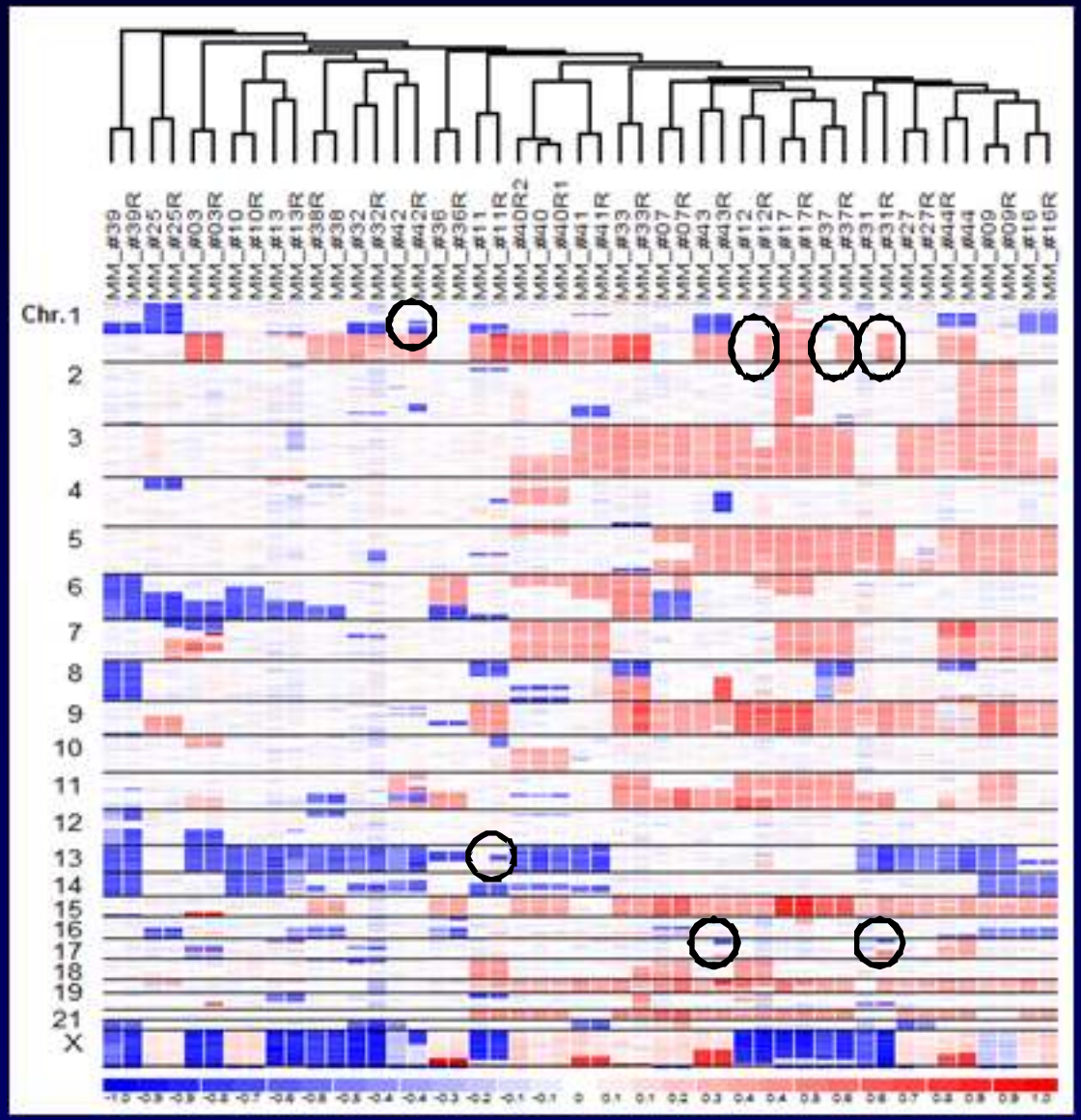
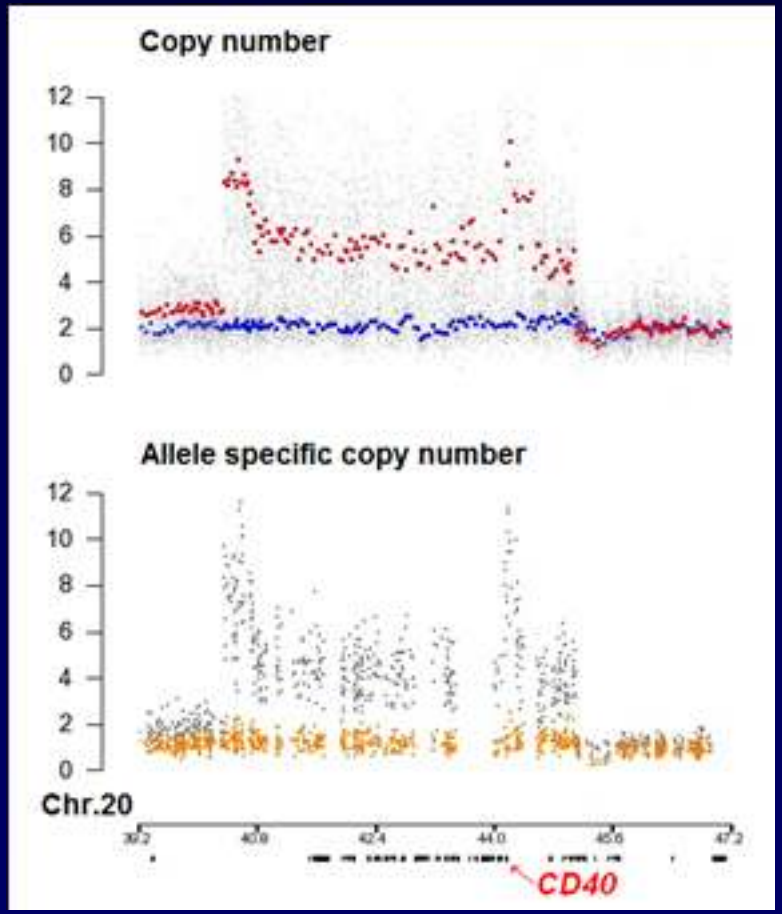


Pathways targeted at relapse

- **NF-κb activation (25% of the MM)**
  - ✓ Amplification of activator (*CD40*)
  - ✓ Homozygous deletion of repressors (*CYLD*, *TRAF3*, *cIAP1/2*)

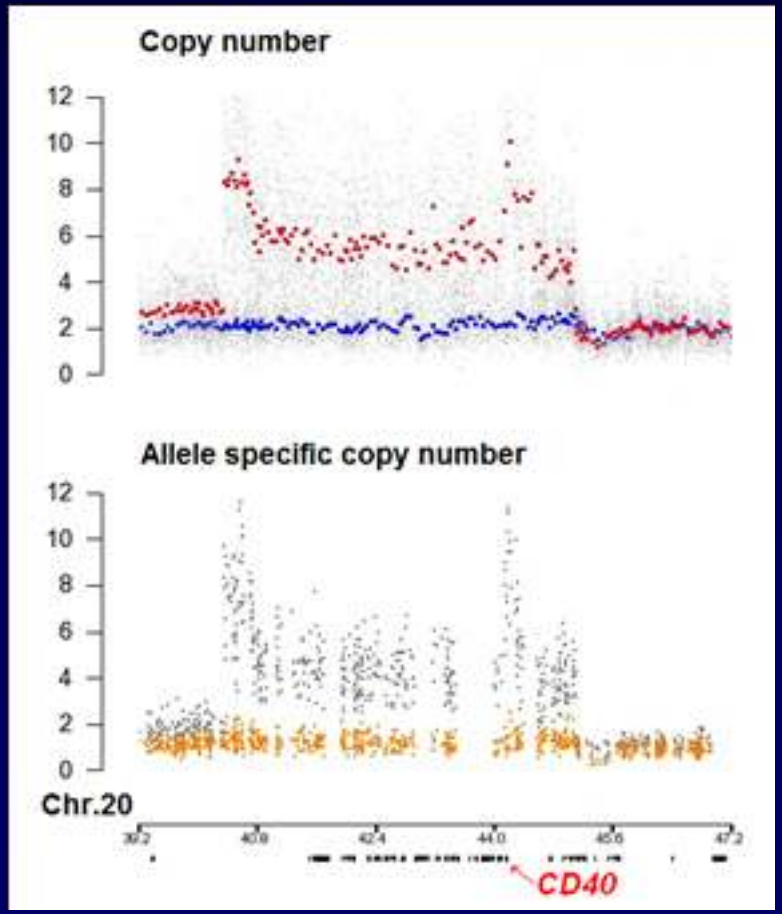
NF-κb signaling activation

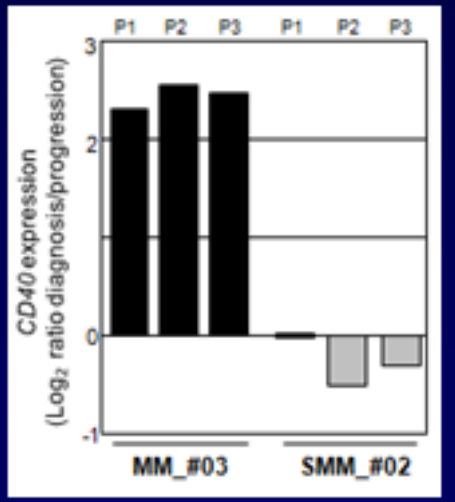
- Amplification of *CD40*



NF-κb signaling activation

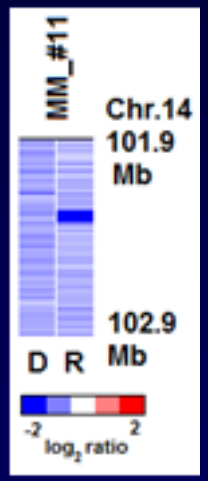
- Amplification of *CD40*

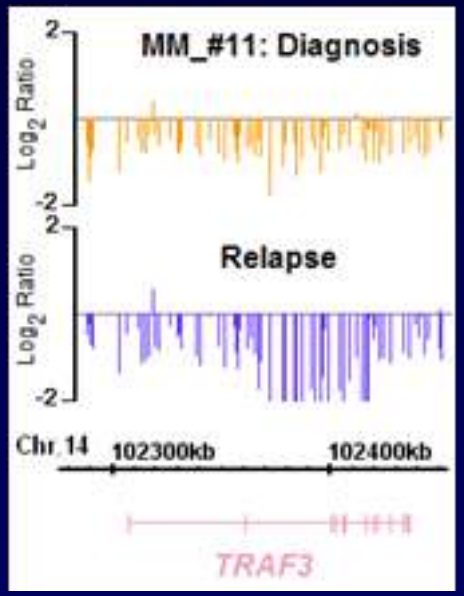




NF-κb signaling activation

- Homozygous deletion of *TRAF3*





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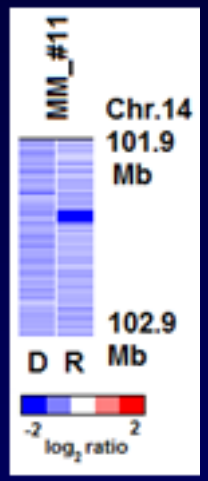
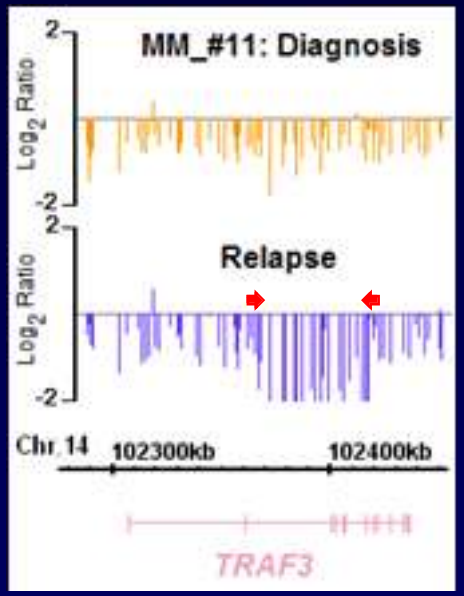
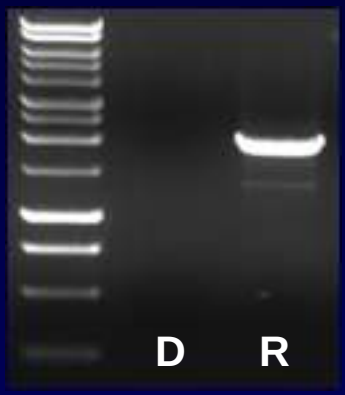




MM_#11



NF-κb signaling activation

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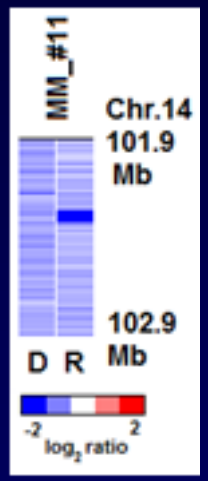
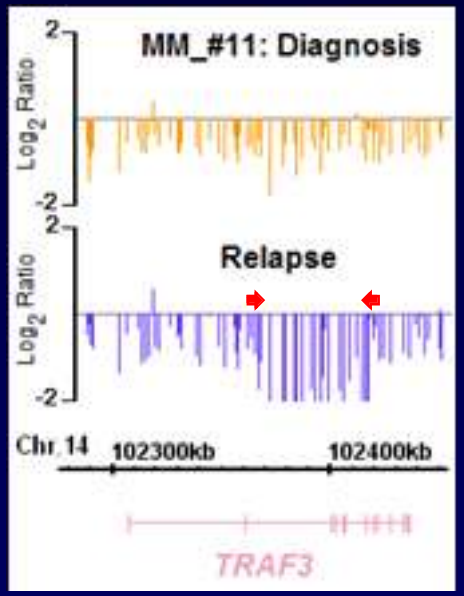
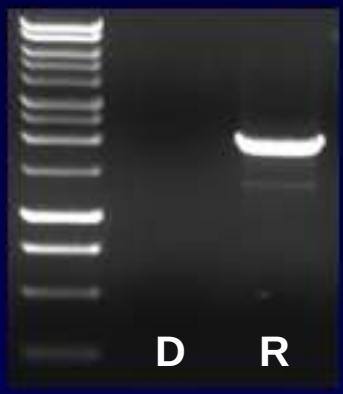


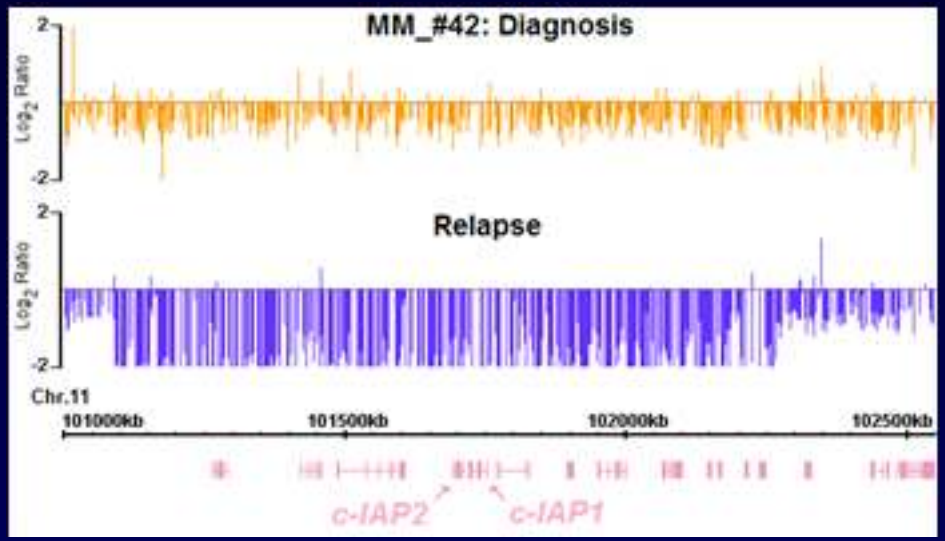


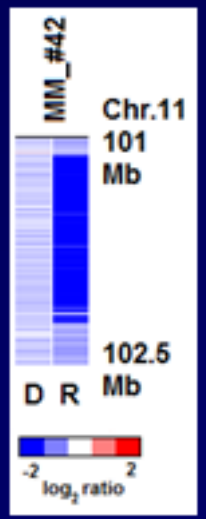
MM_#11



NF-κb signaling activation

- **Homozygous deletion of *cIAP1/2***





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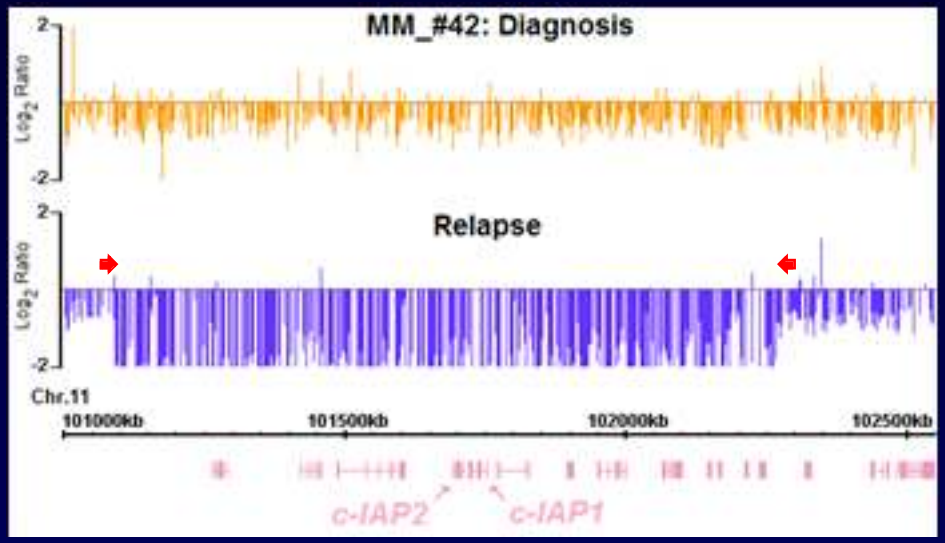

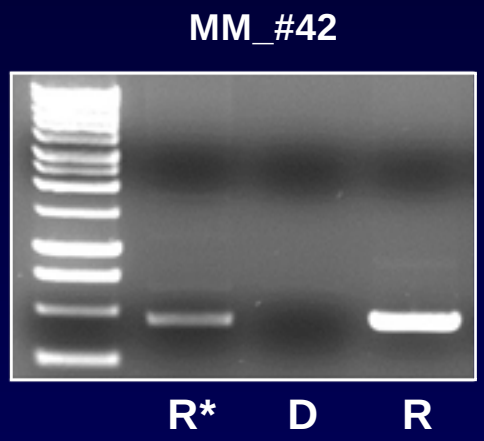

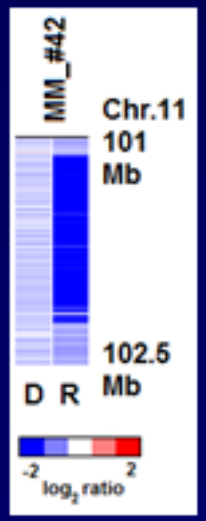

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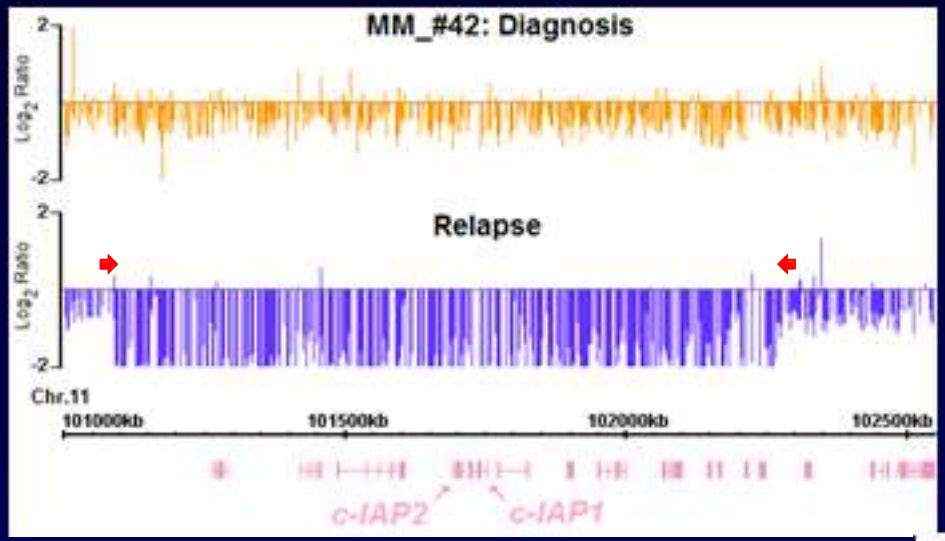
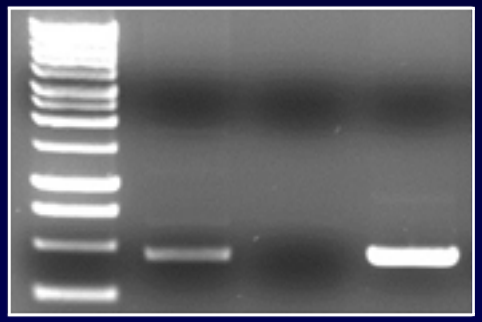
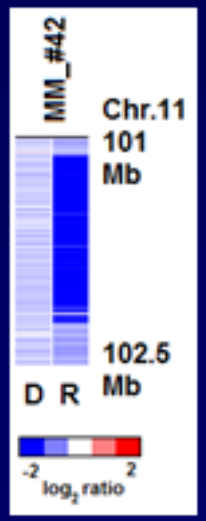
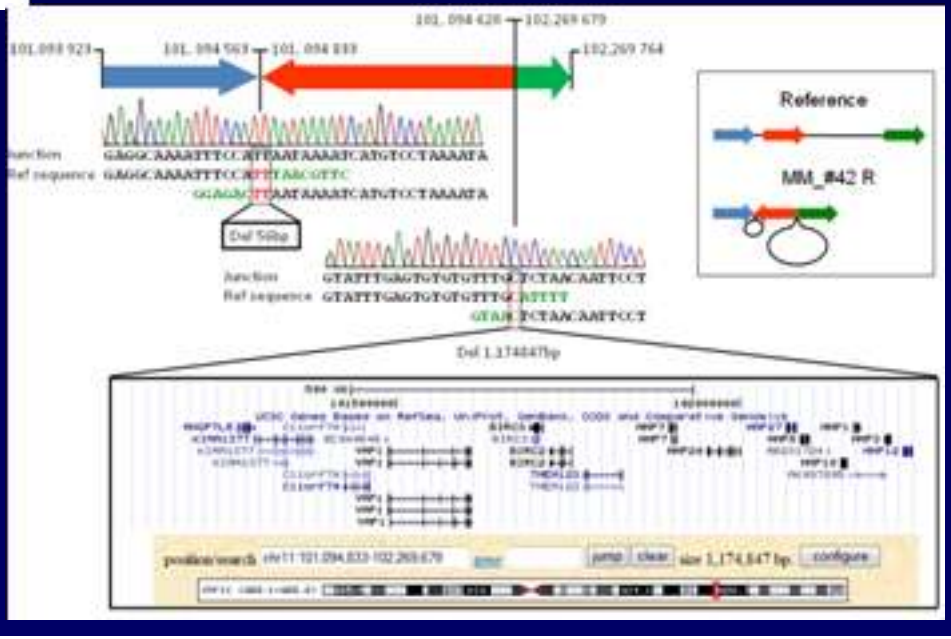


MM_#42

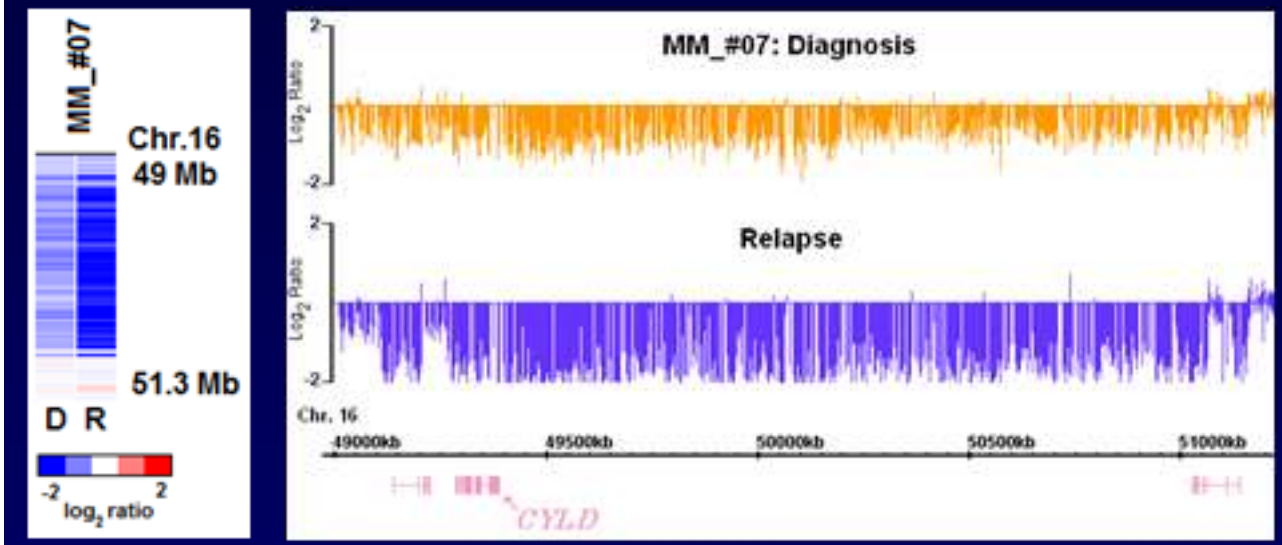






NF-κb signaling activation

- Homozygous deletion of *CYLD*



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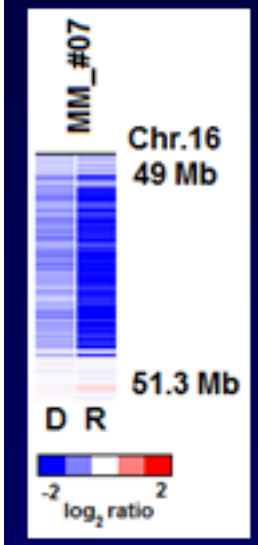
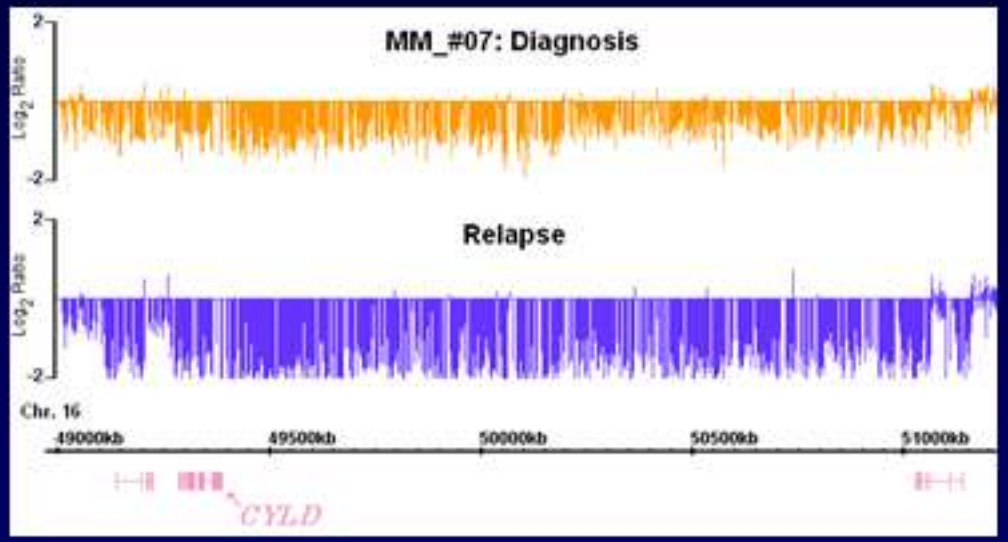
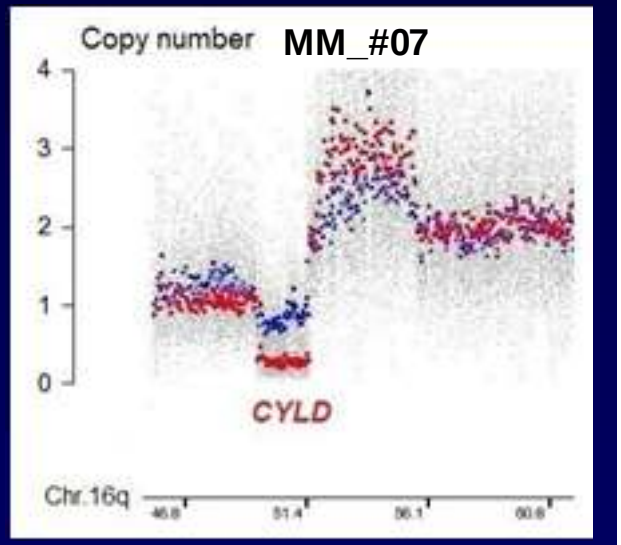




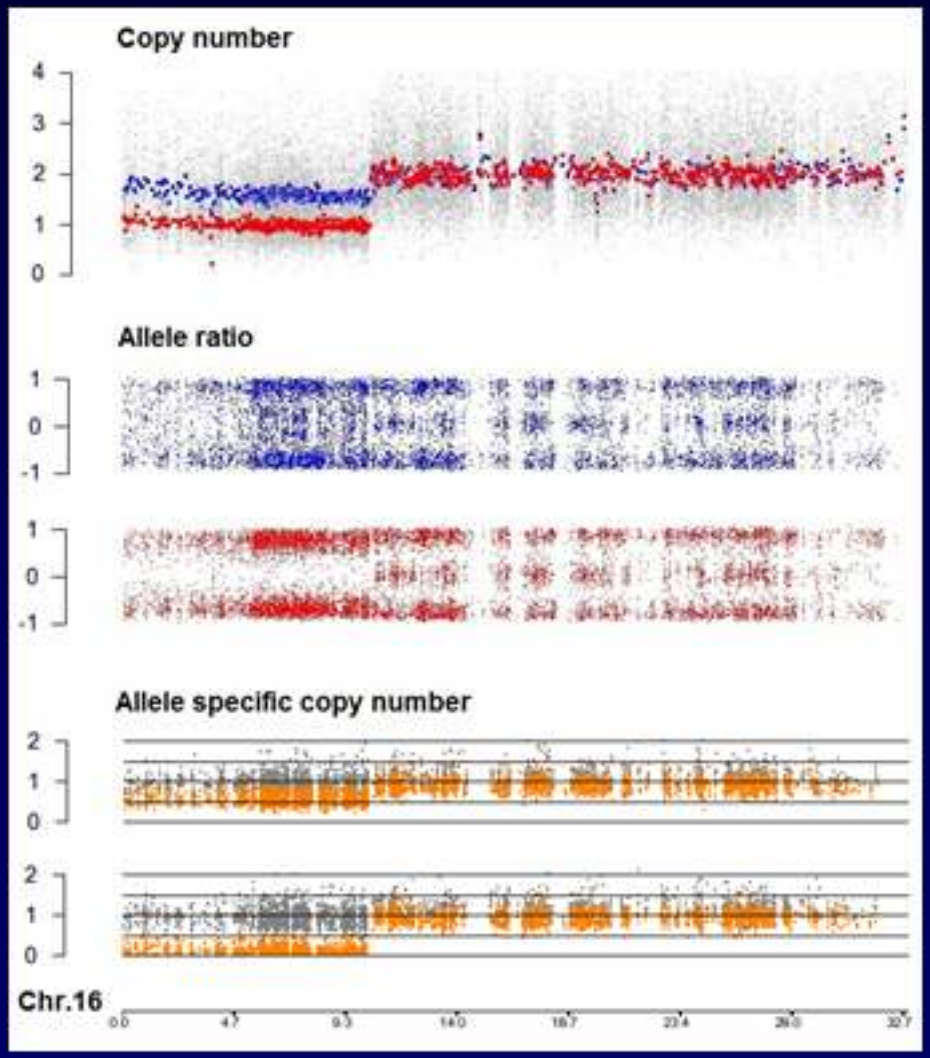


Conclusion (I)

- **NF-κb pathway is frequently targeted by relapse-associated CNAs**
- **Genomic instability persists at relapse:**
  - Significant increase in CNAs at relapse (15.8 vs. 19.1, p= 0.002)
  - Two patients acquired new rearrangements at relapse generated by two different mechanisms of DNA repair
- **A minor subclone with biallelic *CYLD* deletion outcompeted the predominant diagnostic clone**
- **Is selection of minor subclone a common phenomenon at relapse ?**

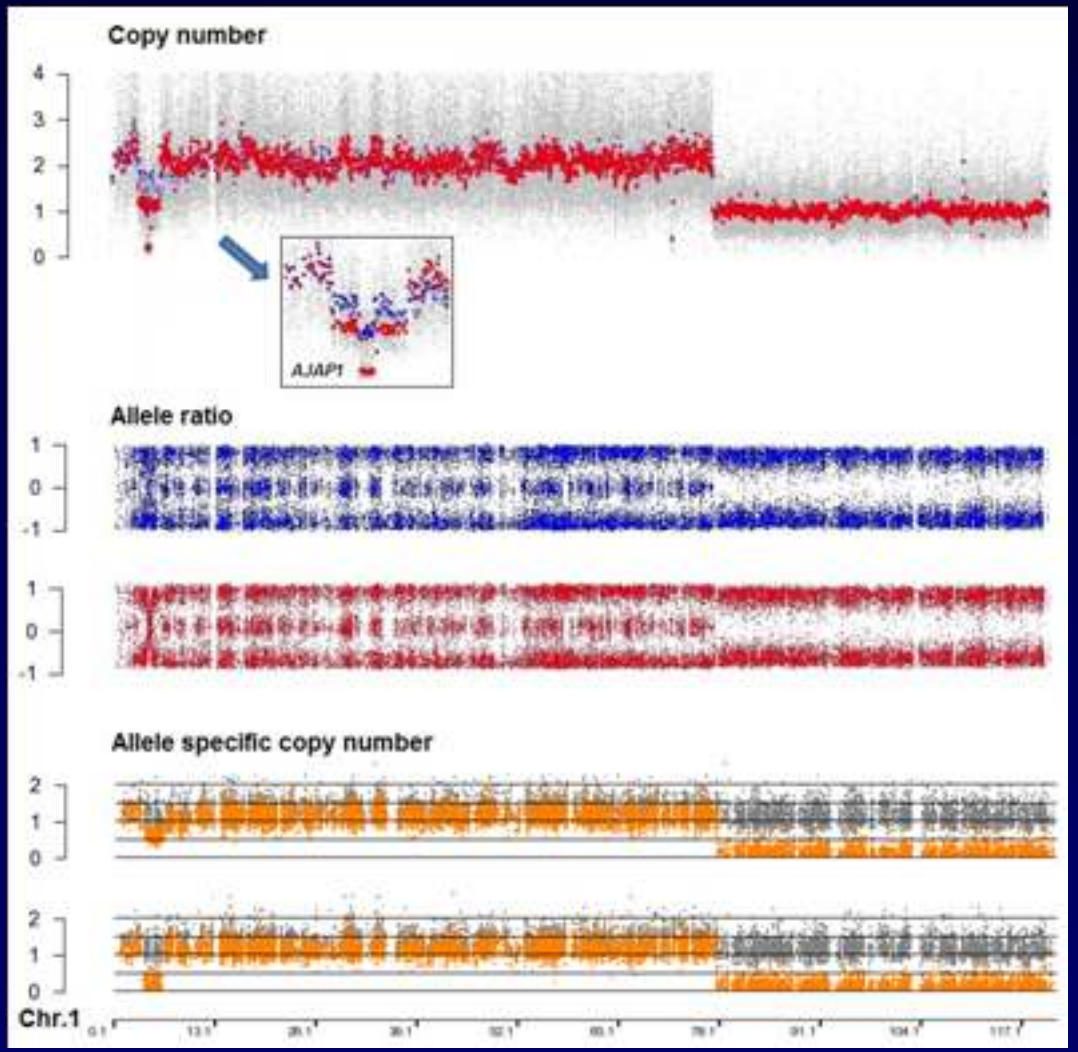
Selection of subclones after initial therapy

- **Deletion at 16p**



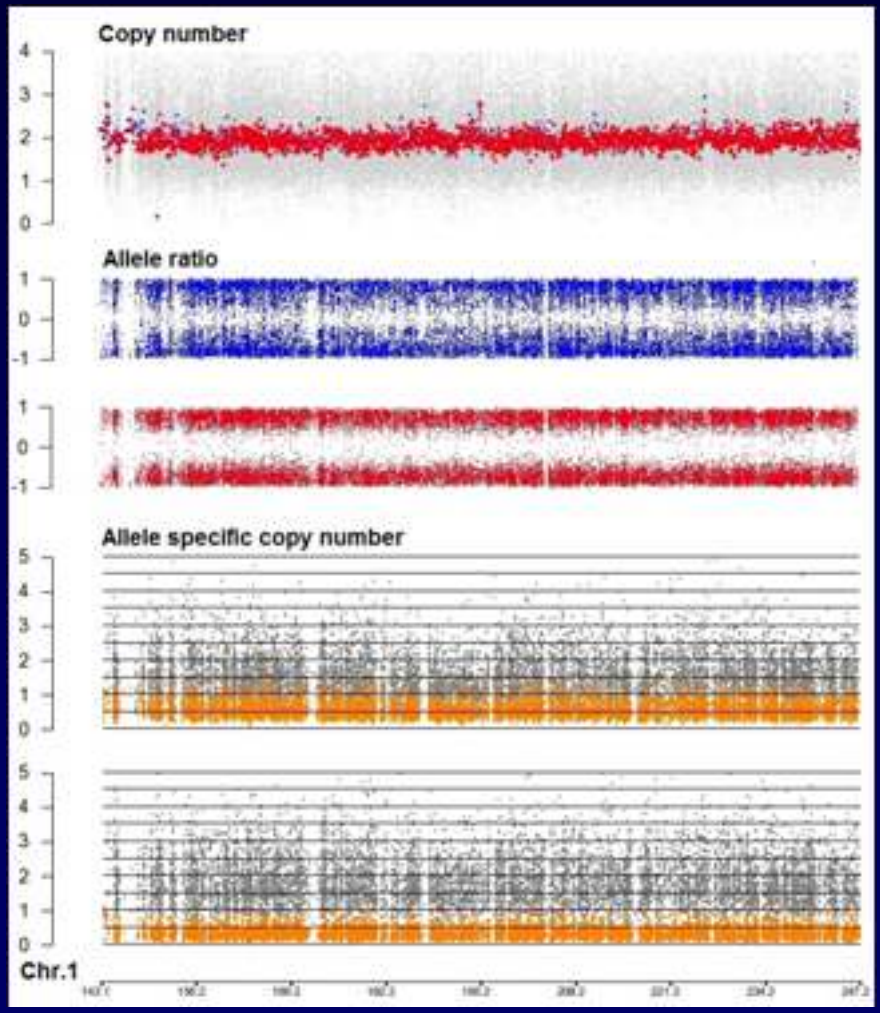
Selection of subclones after initial therapy

- **Biallelic deletion of *AJAP1***



Selection of subclones after initial therapy

1q UPD



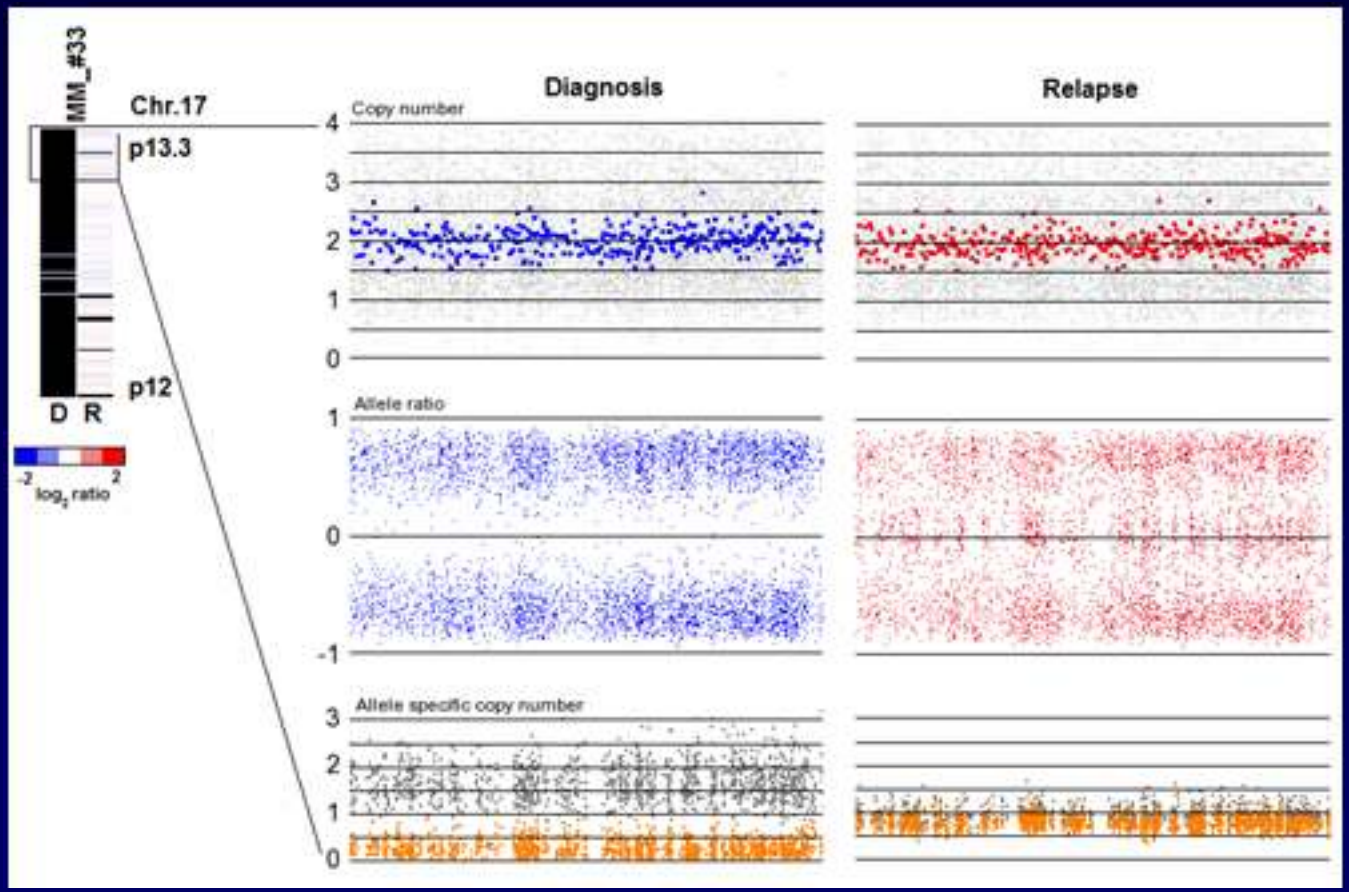
Conclusion (II)

- MM at diagnosis is often composed of genetically disctinct subclones present in varying proportions
- Minor subclones at initial presentation are often the source of major clones that recur after treatment

- Are relapse clones evolving from diagnostic clones or from ancestral clones?

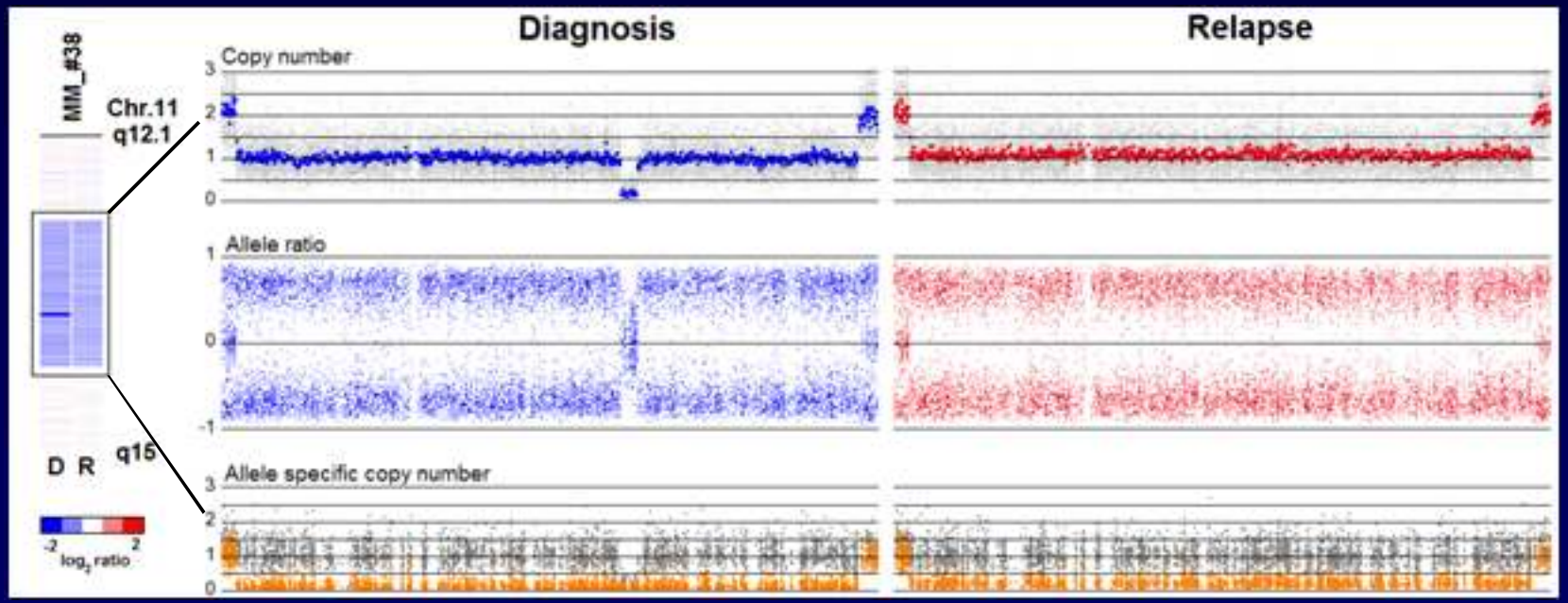
Loss of lesions after initial therapy

UPD loss



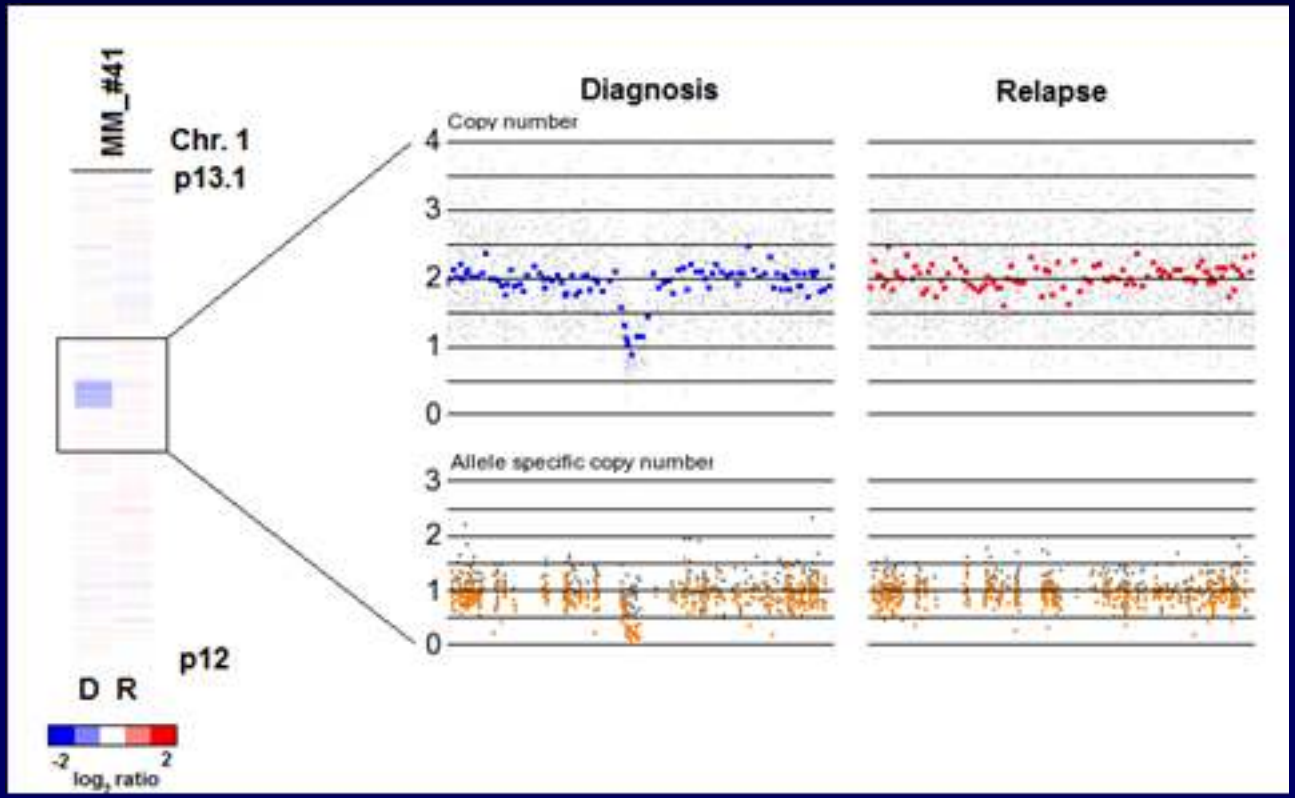
Loss of lesions after initial therapy

- **Biallelic deletion loss**



Loss of lesions after initial therapy

- **Deletion loss**



Conclusion (III)

- In one third of the patients, the dominant clone at relapse originates from a subclone that shared most of genetic lesions with the dominant diagnostic clone but did not evolve from it
- The ancestral clone gave rise to different subclones that evolve independently by acquiring new CNAs

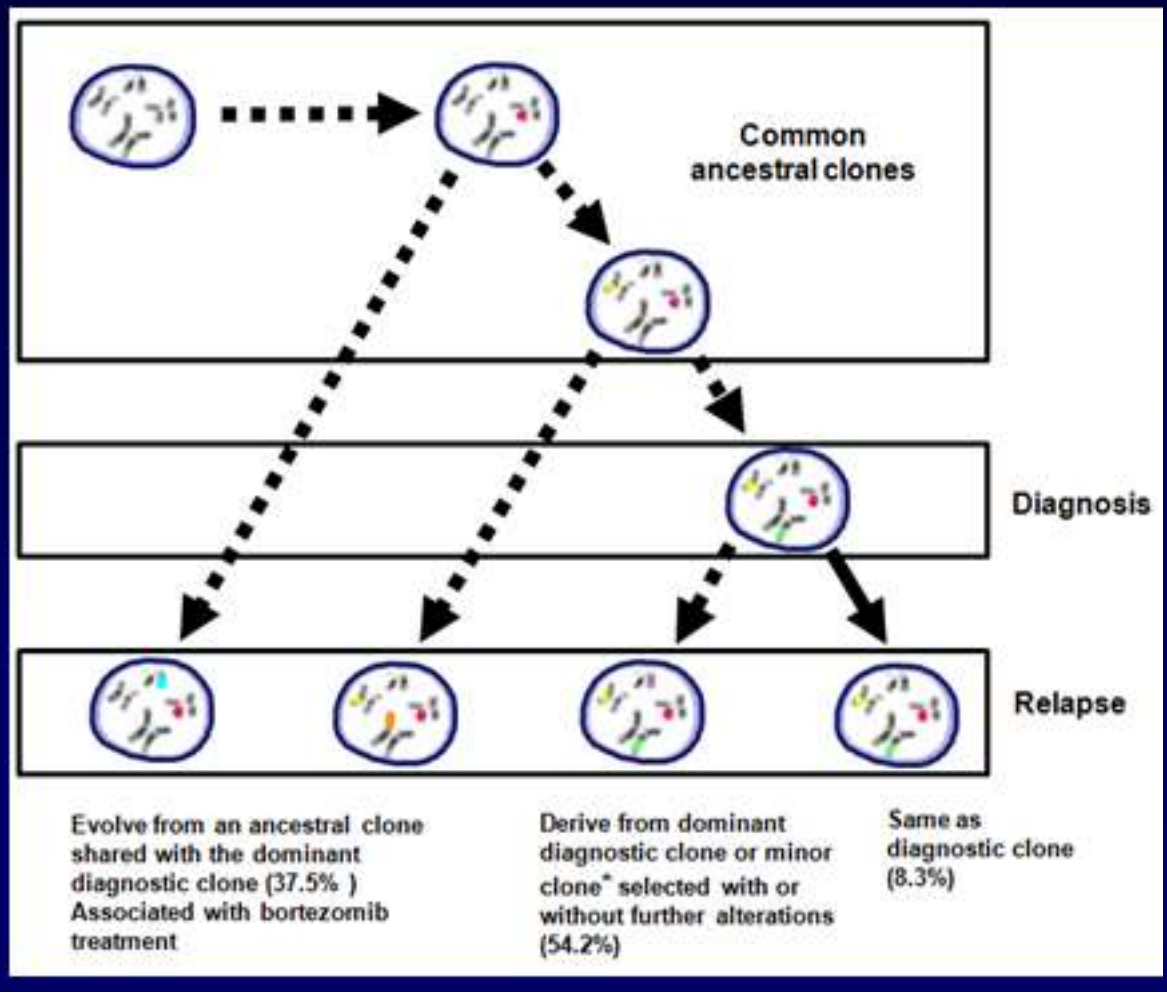
- Is emergence of an evolutionary past clone associated with a type of treatment?

Treatment

- **Expansion of evolutionary past clone is almost exclusively identified in patients treated with bortezomib (p= 0.009)**
- **Ancestral minor clones survive bortezomib therapy, evolve and expand leading to relapse**
- **Two explanations**
  - The clone is more aggressive in response to bortezomib
  - Bortezomib treatment specifically extinguishes the dominant subclone carrying the “driver” mutation that manifests as the symptomatic myeloma while other subclones persist, thus minor subclones which are not initially competitive against the dominant population cells have a chance to thrive and acquire new anomalies.

Evolutionary relationship between diagnostic and relapse MM samples

- At least three evolutionary models



Genetic progression in MM

- Remarkable adaptive changes driven by two forces, genomic instability and clonal selection in response to drug selection pressure
- At diagnosis, genetically distinct subclones already possess variably aggressive growth properties
- Suggests new treatment paradigm that would combine targeted therapy and subpopulations control to eradicate all myeloma subclones in order to obtain long-term remissions

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