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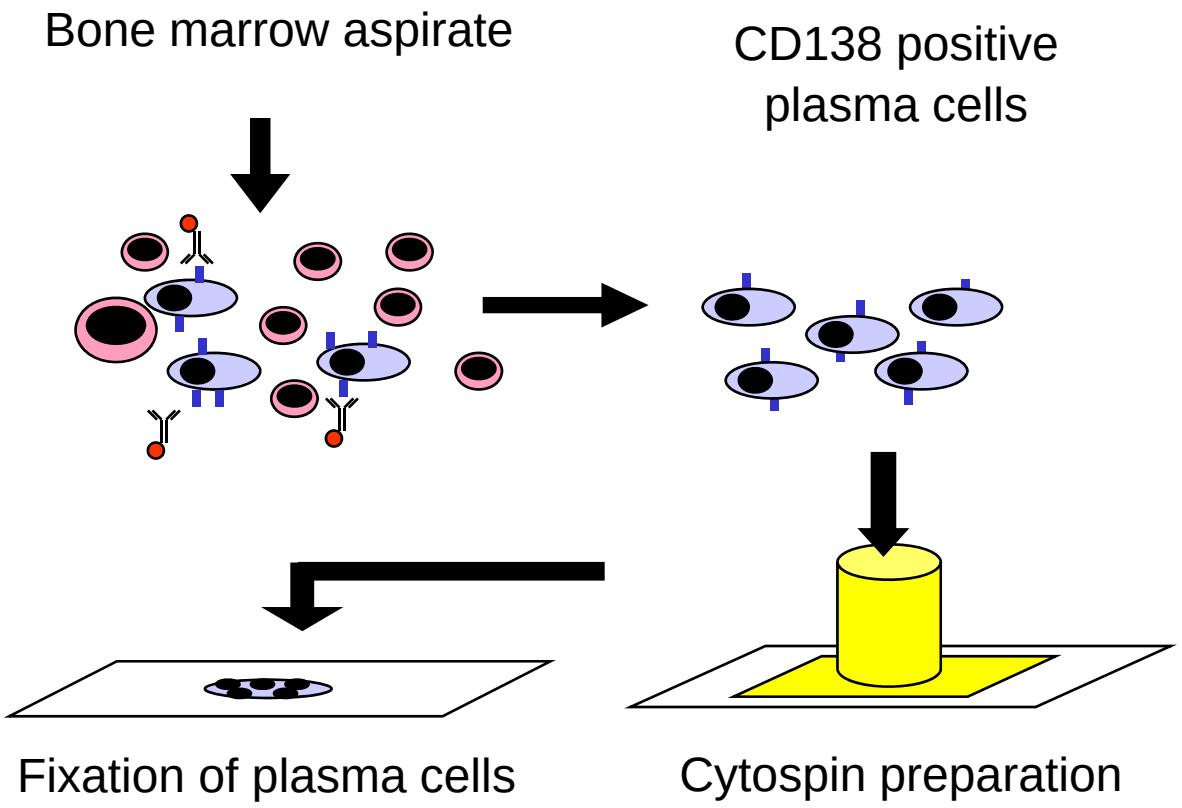
Genetic diagnostics in plasma cell disorders

Genetic Background

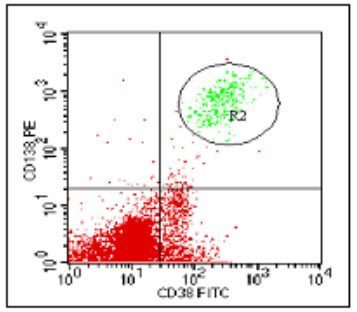
From the literature it is known that systemic amyloid light chain amyloidosis (AL) shares chromosomal changes with other monoclonal plasma cell disorders such as multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS)

Methods

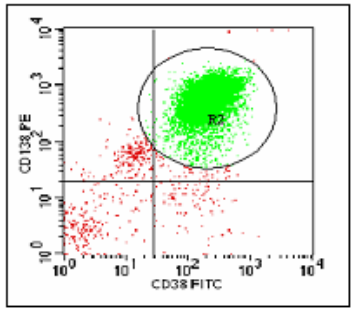
Enrichment of CD138 positive plasma cells by magnetic activated cell sorting (MACS)



Flow cytometry



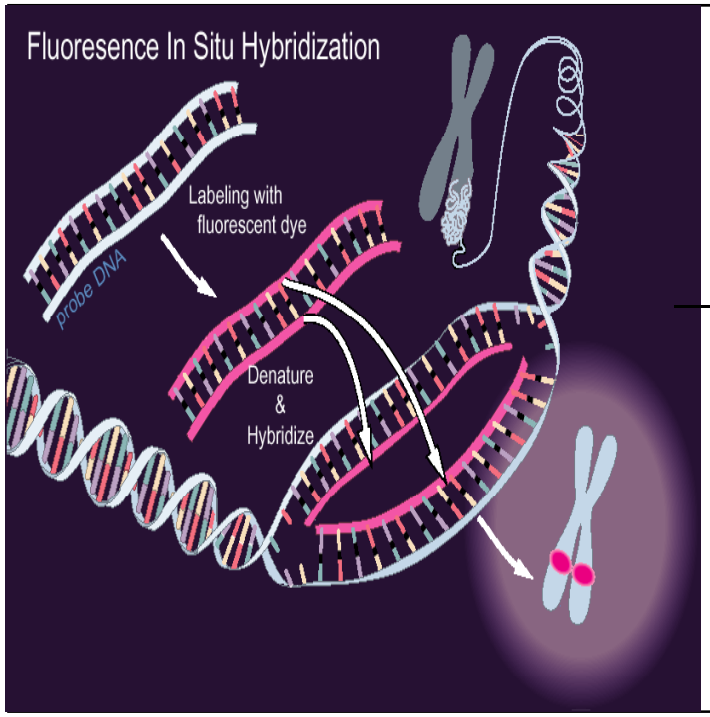
3.8% CD138+

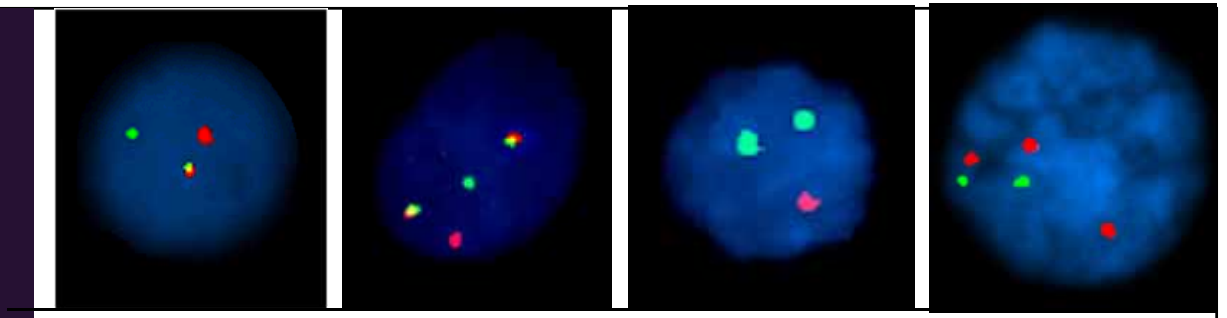


97.2% CD138+

Methods

Interphase fluorescence *in situ* hybridization (FISH)





<u>IgH translocations:</u>

- IgH breakapart
- t(11;14)
- t(4;14)
- t(14;16)

<u>Deletions:</u>

- 8p21
- 13q14
- 17p13

<u>Gains</u>:

- 1q21
- 5p/5q
- 9q34
- 11q23
- 15q22
- 19q13

Interphase-FISH in multiple myeloma

Standard method to identify MM subgroups

(1) hyperdiploid

accumulation of extra copies of chromosomes 5,9,11,15, and 19

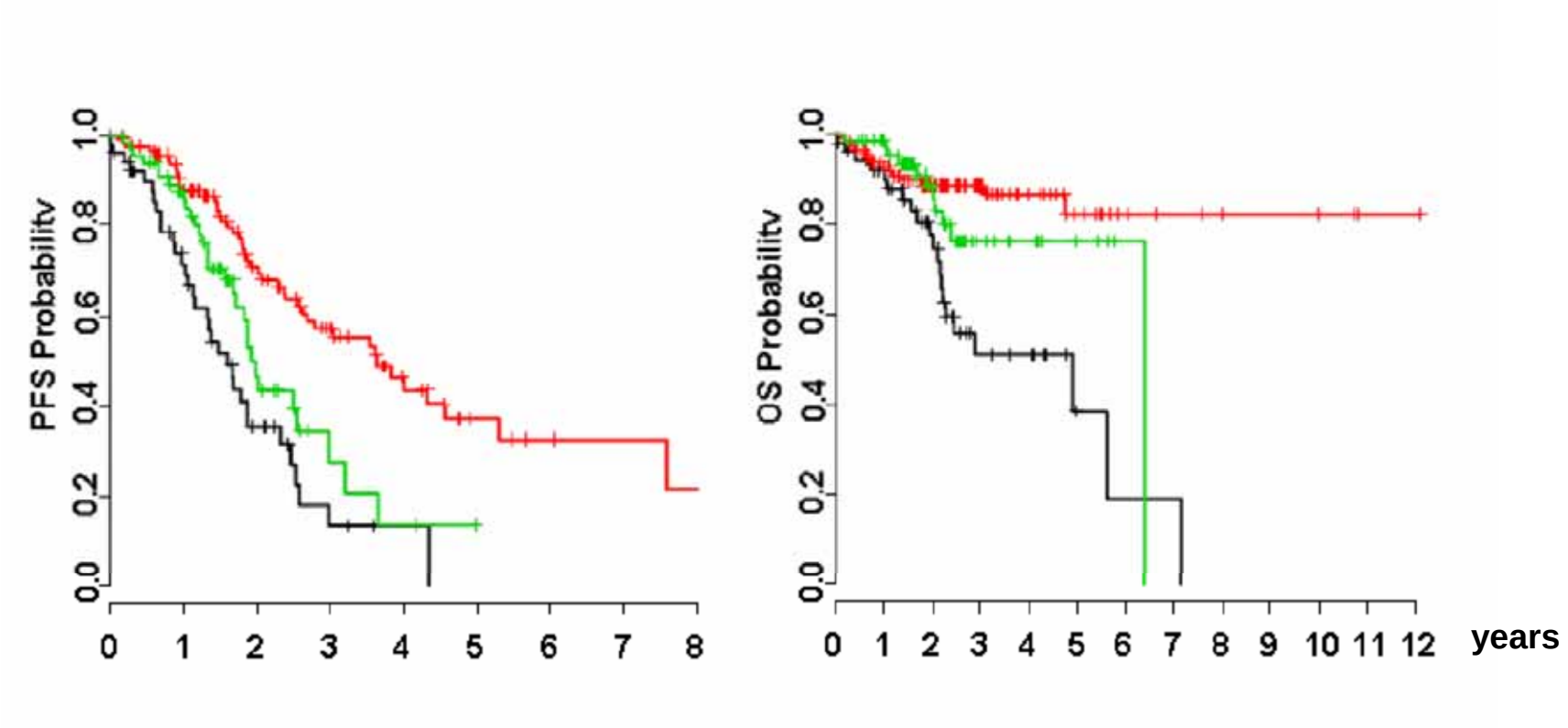
(2) non-hyperdiploid

translocation t(4;14) or t(14;16) frequently associated with deletions 8p21,13q14,and 17p13

(3) translocation t(11;14)

(4) gain 1q21

FISH based risk score in multiple myeloma



Favorable:	hyperdiploid subgroup, t(11;14)
Intermediate:	del 13q14 and/or +1q21
Poor :	del 17p13 and /or t(4;14) or t(14;16)

Intention

- To evaluate the cytogenetic aberration pattern in a larger cohort of AL amyloidosis patients
- To compare the aberration pattern with data from patients with MGUS and MM
- To correlate specific chromosomal aberrations in AL amyloidosis patients with hematological and clinical parameters

Bochtler et al., 2008, Blood 111:4700-4705

Patients characteristics

Overall study group: 231 patients

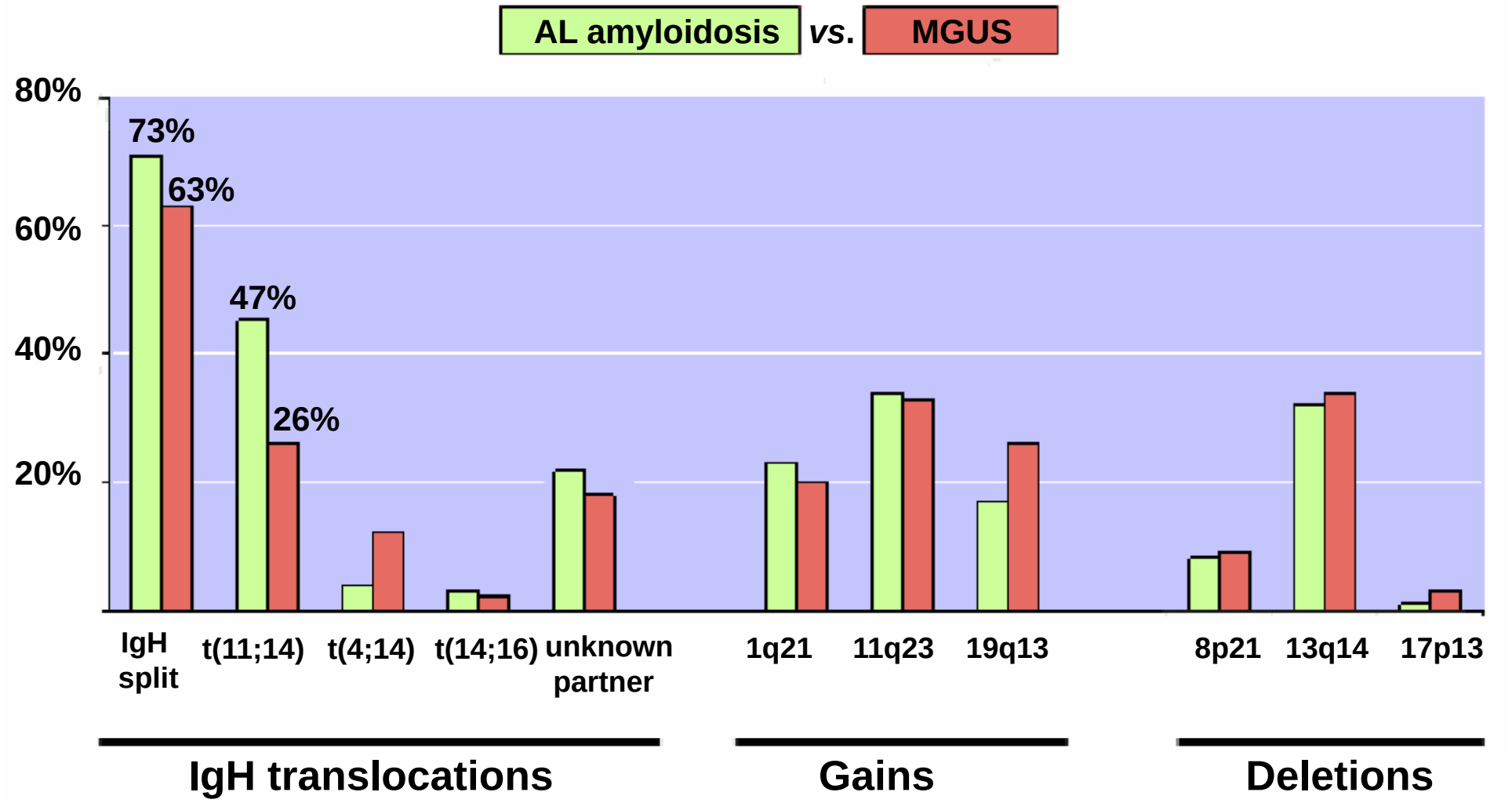
4 Groups:	AL	(n= 75)
	AL + MM stage I	(n= 10)
	MGUS	(n= 127)
	MM stage I	(n= 19)

Mean age: about 60 years

Median plasma cell content: ~ 10% in AL & MGUS
~ 20% in MM stage I

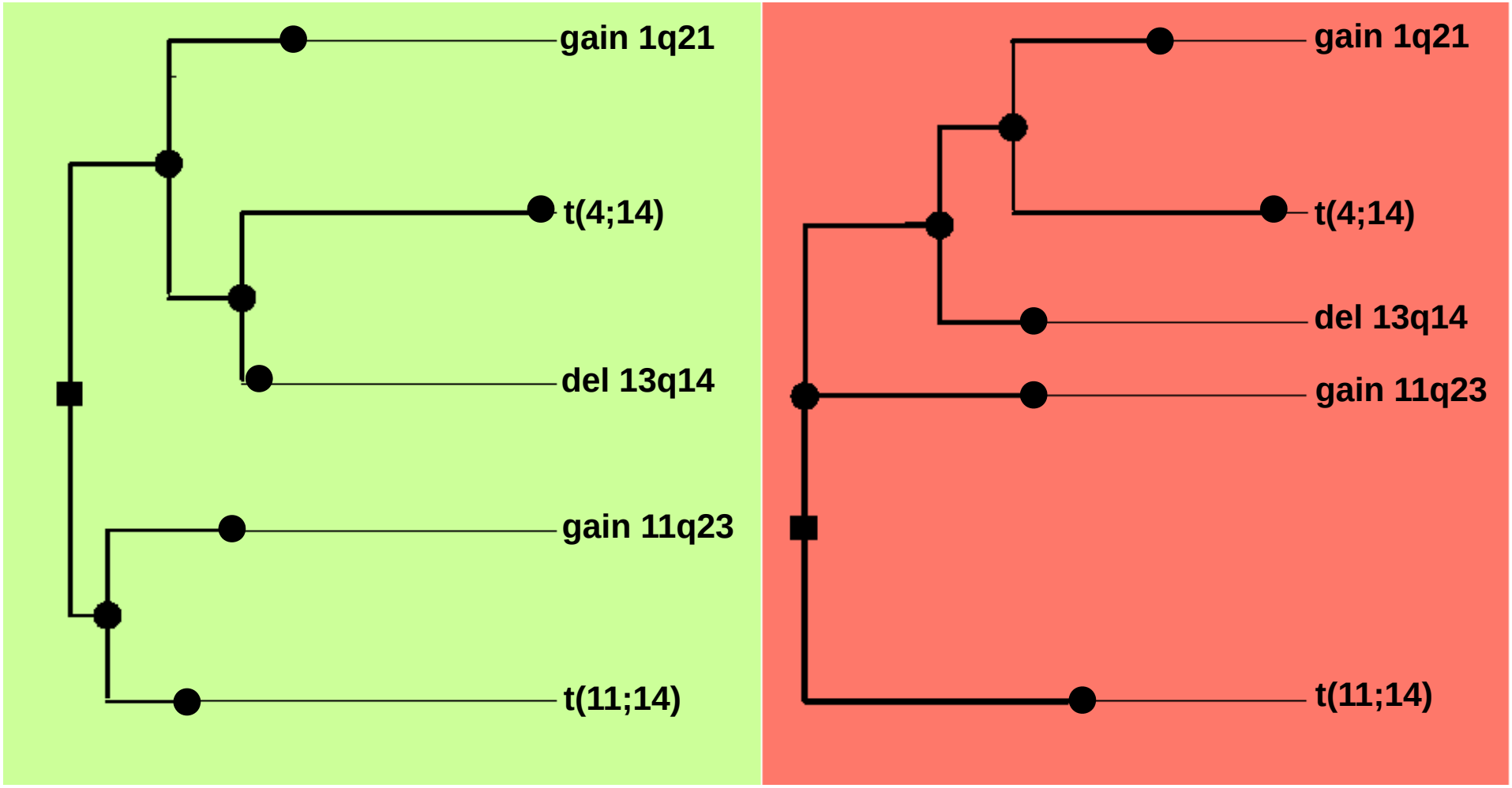
Lambda light chain: predominance in AL

Frequency of chromosome aberrations detected by interphase FISH



Clustering of chromosome aberrations

Oncogenetic tree model



AL amyloidosis **MGUS**

Correlation with hematological parameters

(intact immunoglobulin, kappa vs. lambda light chain restriction, bone marrow plasma cell content)

AL amyloidosis patients

- Translocation t(11;14) is significantly associated with lack of intact immunoglobulin
- Gain of 1q21 is more frequently found in patients with intact immunoglobulin, increased plasma cell content, and significantly more detected in patients with MM stage I

Correlation with clinical parameters

(gender, age, organ involvement, suitability to high dose chemotherapy)

- No significant association of specific chromosome aberrations with clinical parameters
- None of the chromosome aberrations had an influence on the tissue affinity of amyloid fibrils or the severity of the organ involvement

Summary

- AL show basically the same pattern of karyotypic instability as MGUS and MM
- High frequency for translocation t(11;14)
- Significant association of t(11;14) with lack of intact immunoglobulin
- Cyclin D1 upregulation and disruption of the IgH locus might be an important pathogenetic mechanism in AL
- Significant association of gain 1q21 with intact immunoglobulin und progression to MM stage I

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