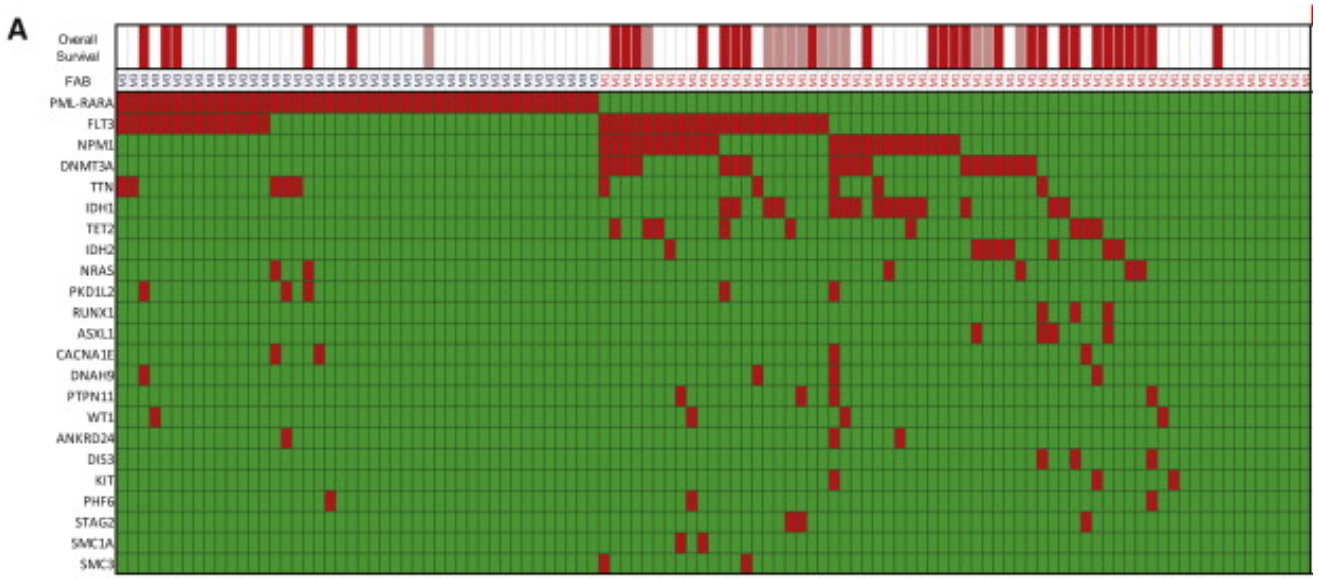
WHOLE EXOME ANALYSIS OF RELAPSING PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

C Bally, J Lehmann-Che, B Cassinat, L Ades, E Letouze, P Hirsch, M-J Mozziconacci, S Raynaud, E Delabesse, M Uzunov, M Hunault, E Lippert, H Lapillonne, C Ferrand, C Gervais, N Gachard, A Guerci, P Fenaux, and H de The

Background

- APL require few other mutations (Welch et al, Cell 2012)



Background

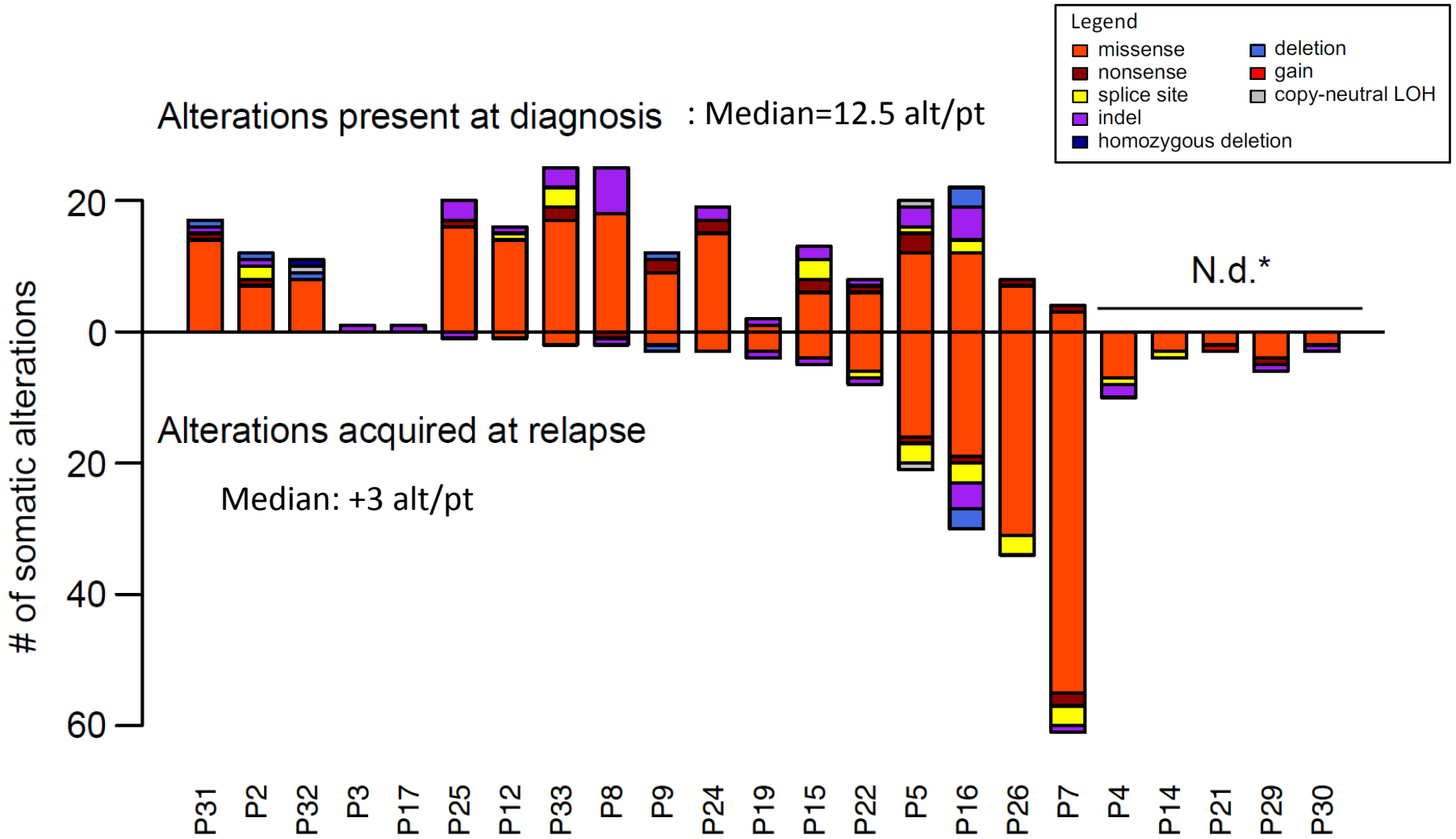
- Most common associated mutations are FLT3 (40%), WT1 (10%), NRAS (10%), KRAS (5%)

- About 20% of patients with APL relapse under ATRA+chemotherapy regimen

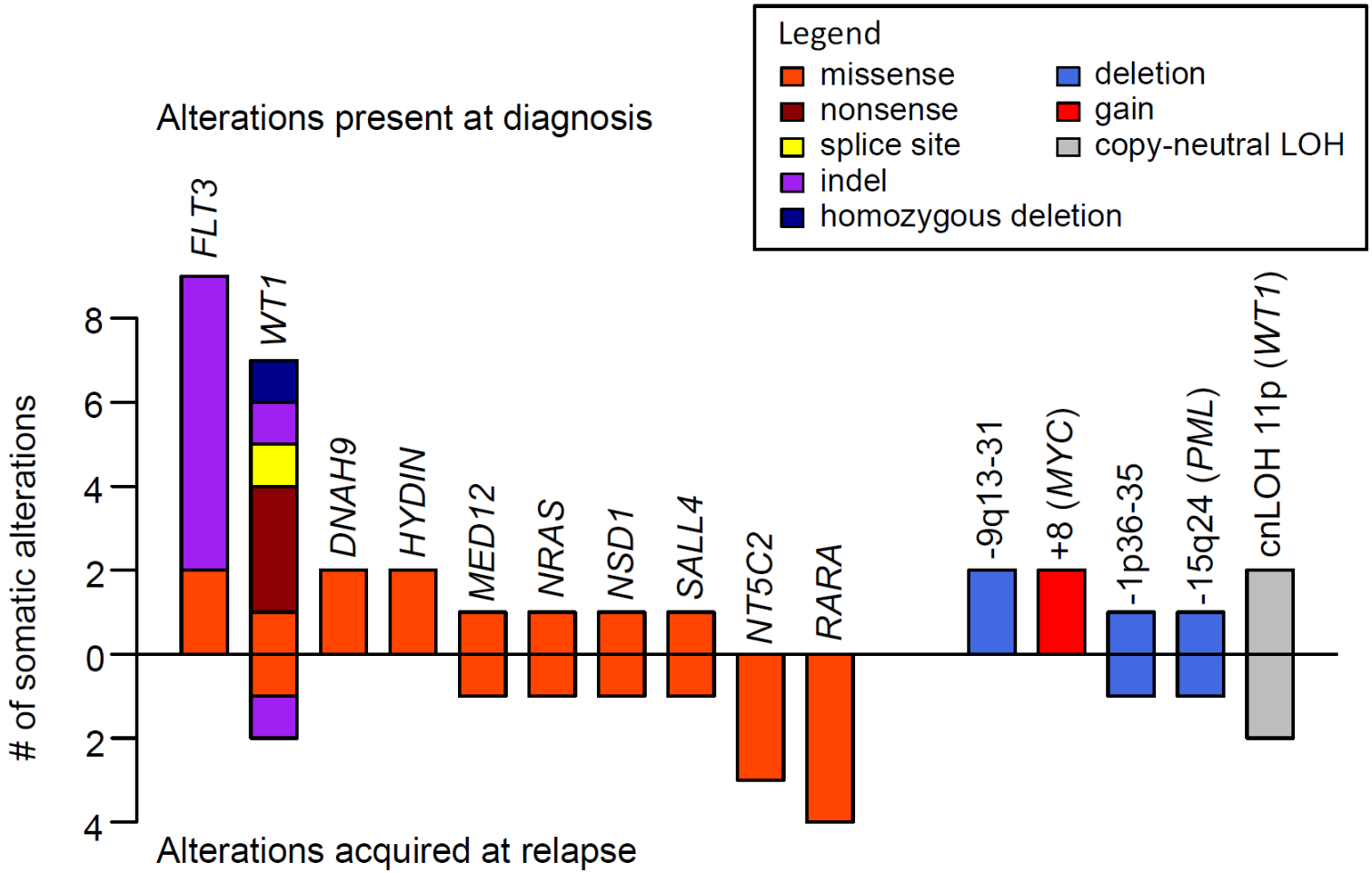
Methods

- Patients with at least one relapse under ATRA +chemotherapy regimen
- French-Swiss-Belgian APL group trials
- Samples at diagnosis, at remission and at relapse (18 trios and 5 duos diagnosis/relapse)
- WES, mean depth of 91X

Number of alterations per patient



Most frequent genetic alterations



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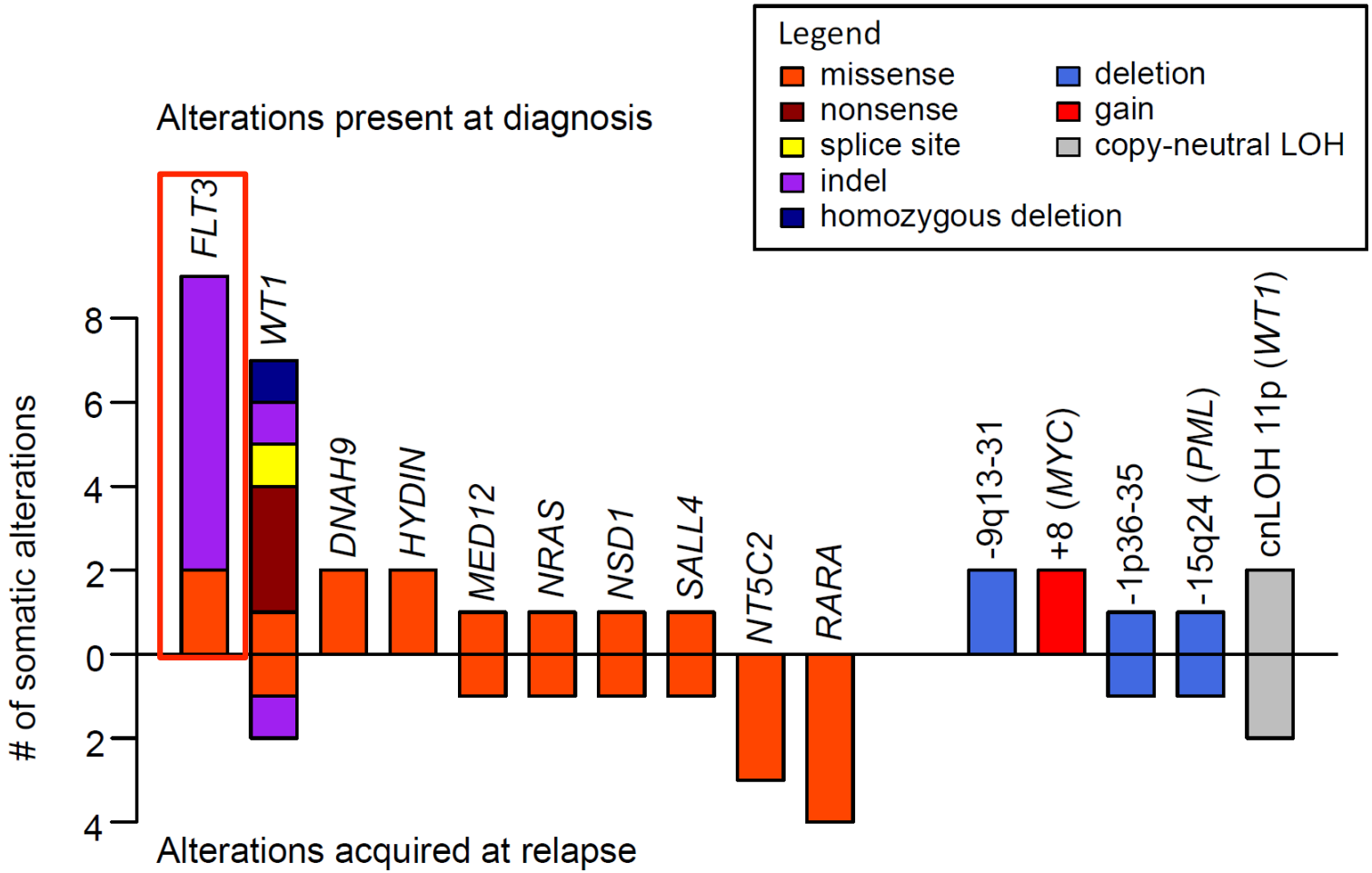

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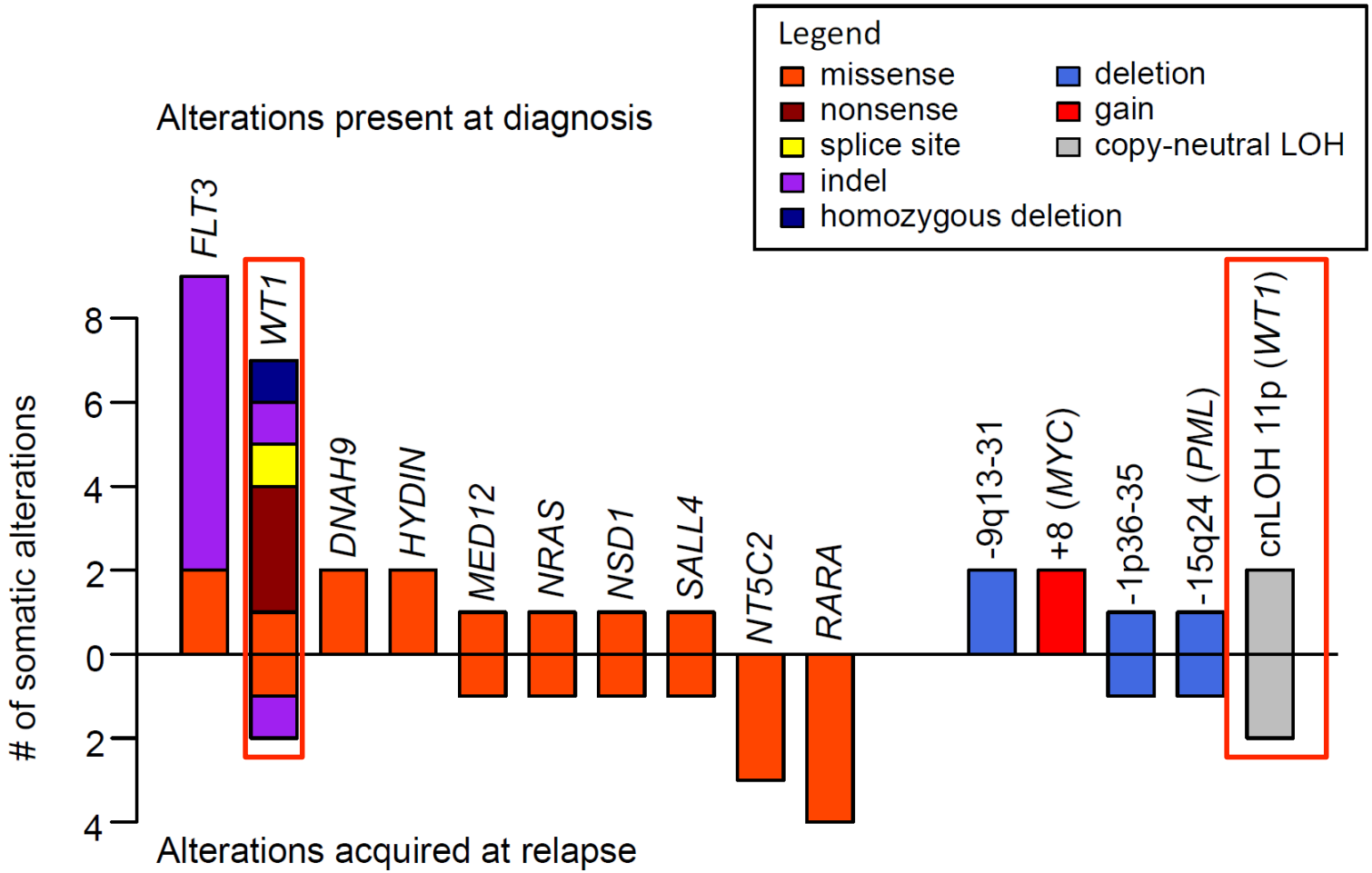

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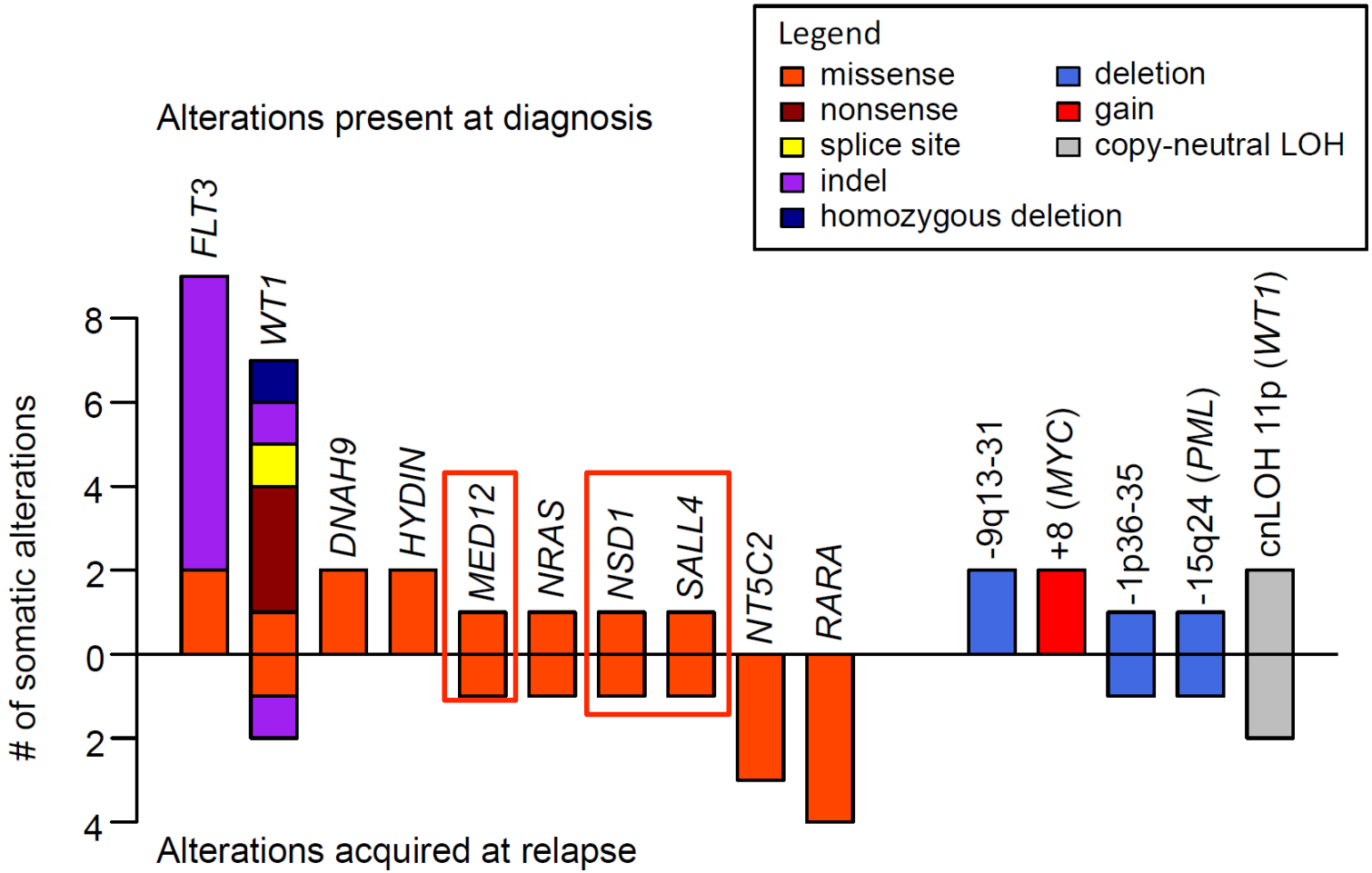

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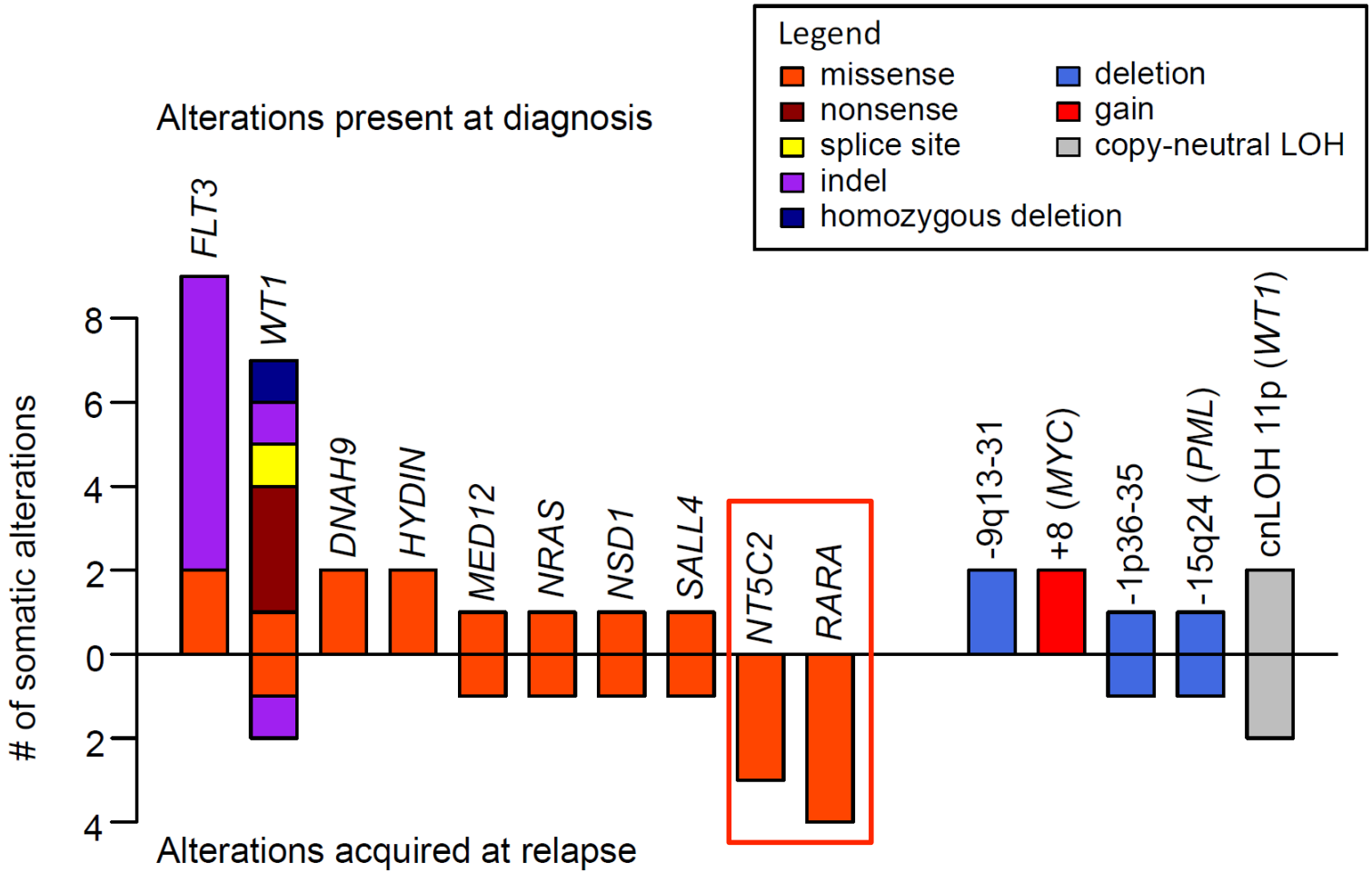

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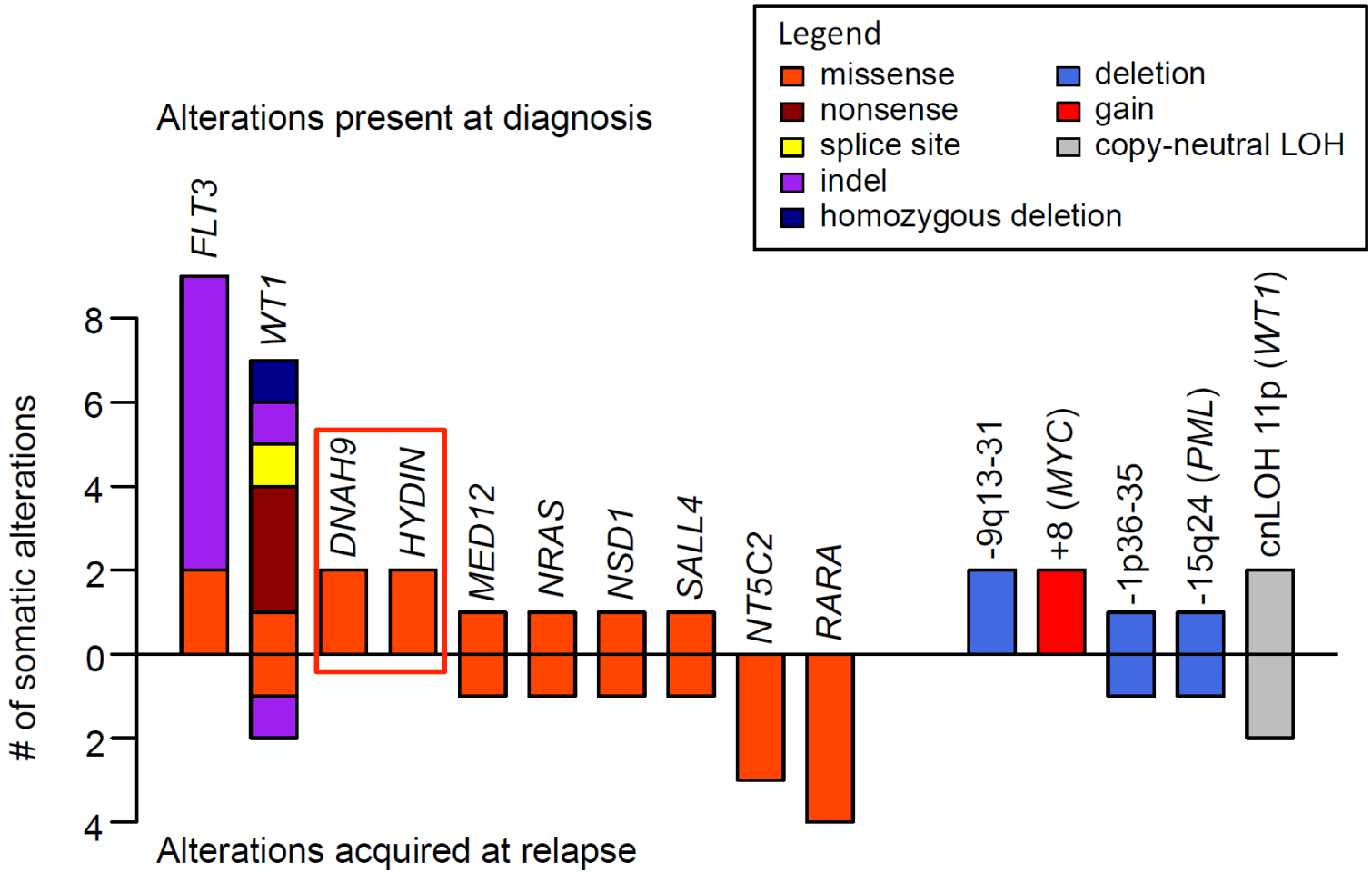

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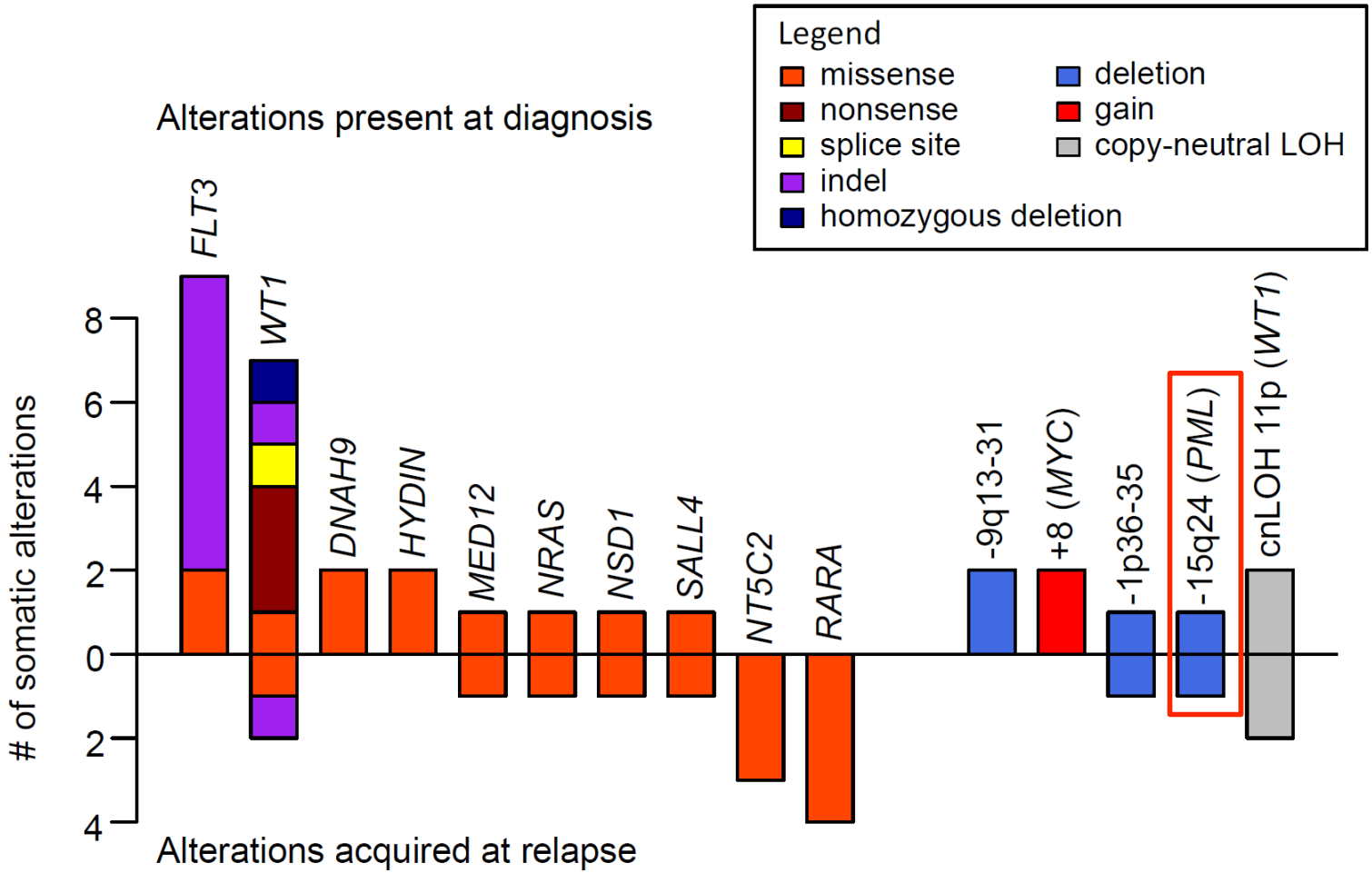
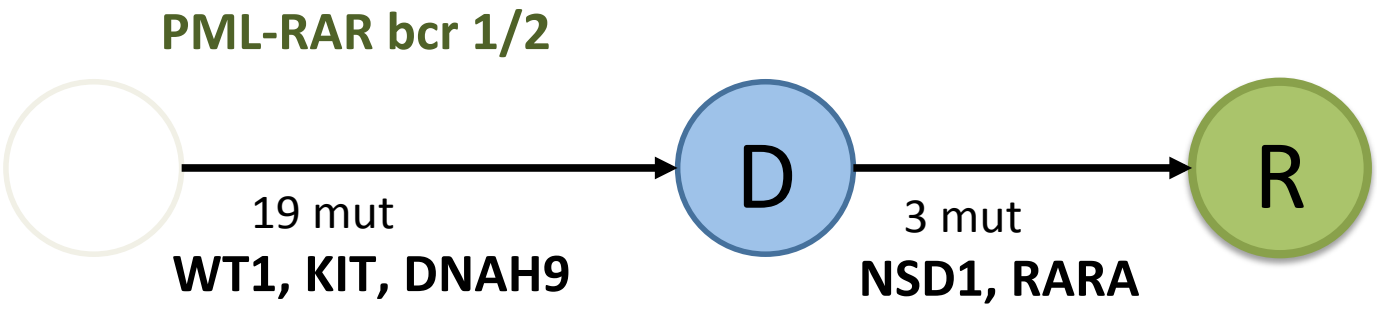


Other genetic alterations

- Mutations affecting MAPK pathway:
  - NRAS (2pts), KRAS (1 pt), BRAF (1 pt)
  - KIT (1 pt)
  - PDGFRA (1pt)

- Genetic alterations affecting transcriptional or epigenetic regulators:
  - WT1 (7 pts)
  - NSD1 (2 pts)
  - ASXL1 (1 pt)
  - MED12 (2 pts)
  - KDM6A (1 pt)
  - TET2 (1 pt)

Linear clonal evolution



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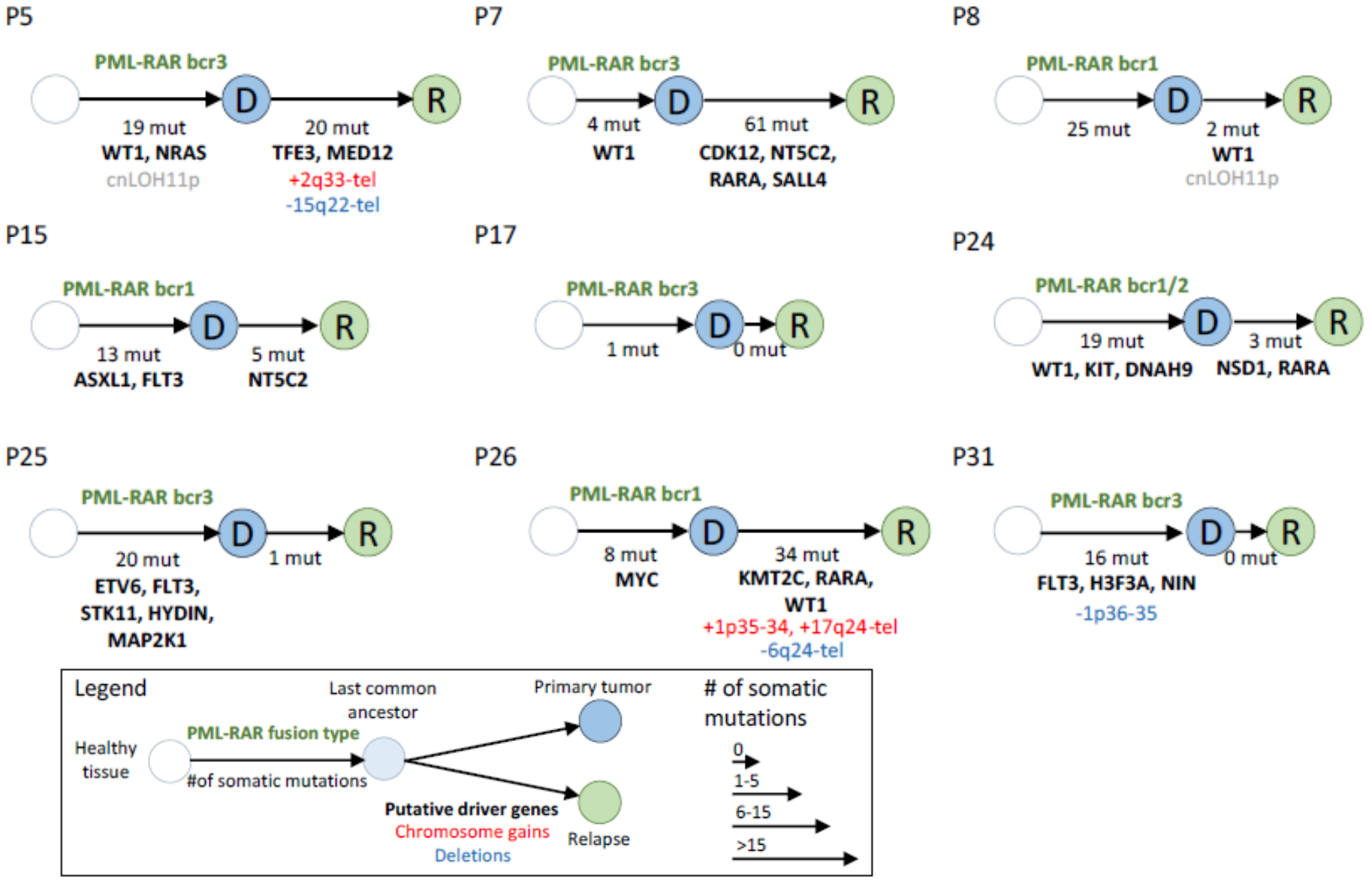
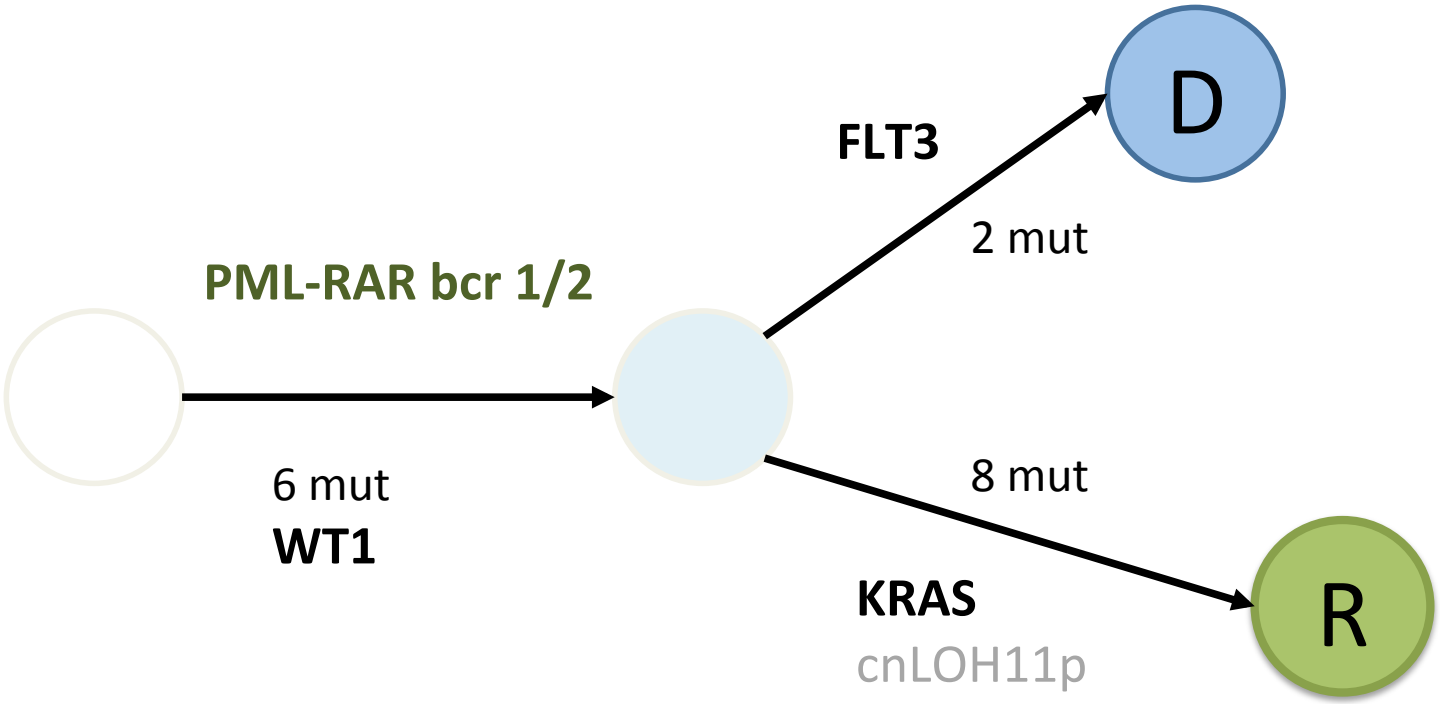


Linear clonal evolution with sub-clonal evolution



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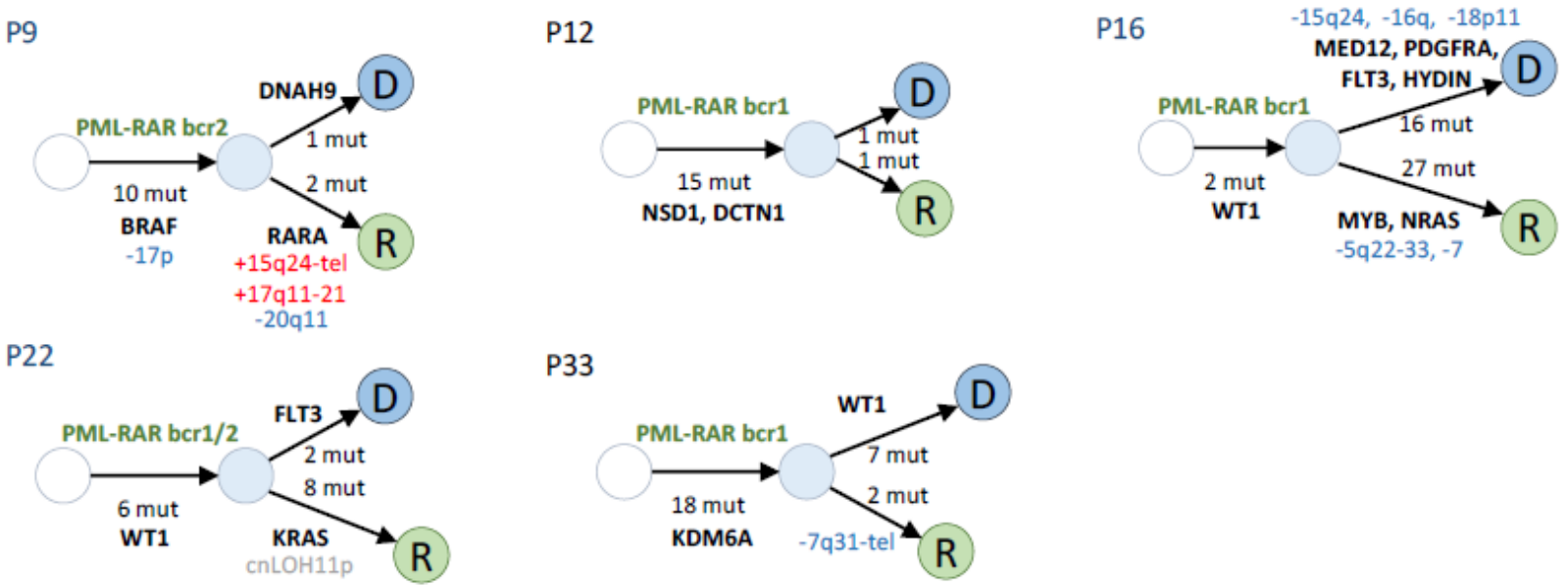
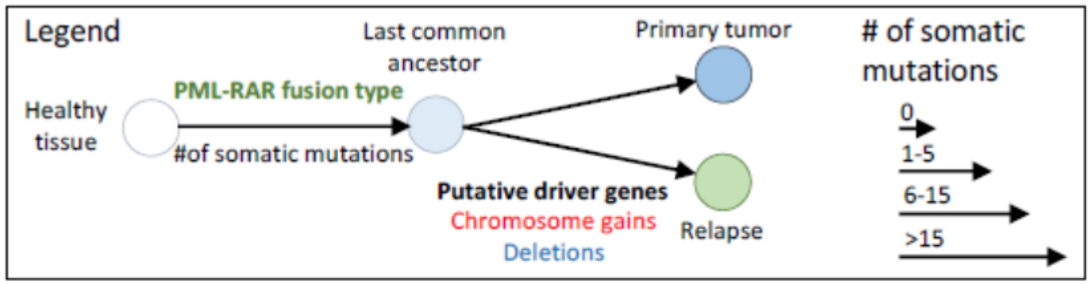
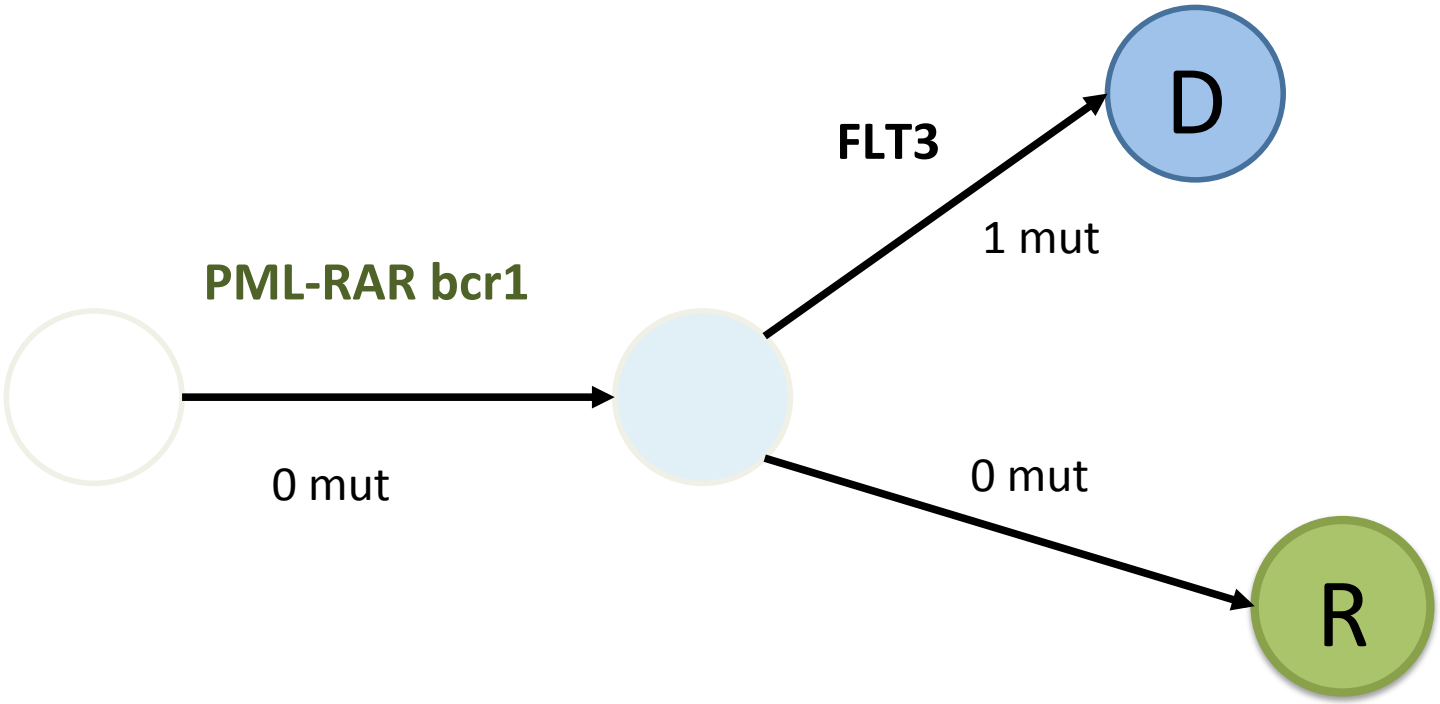




Relapse derive from a pre-leukemic clone



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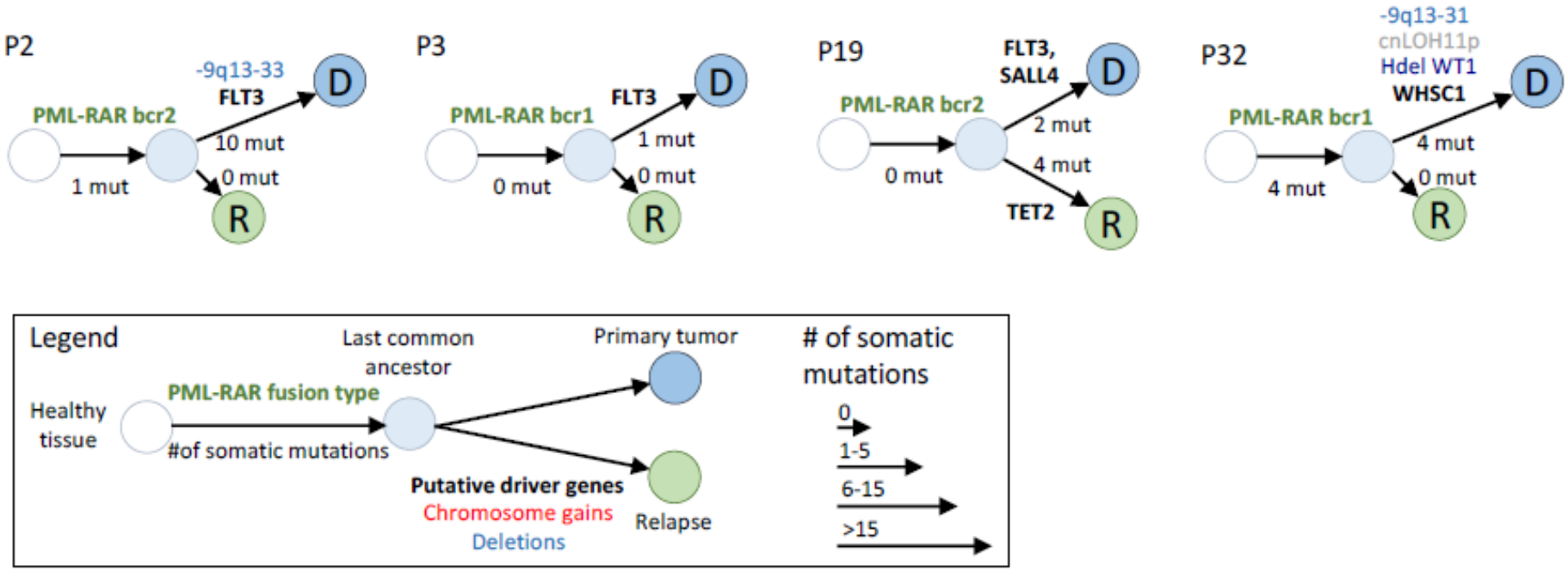

Conclusion

- Few genetic alterations cooperating with PML/RARA in relapsing APL
- High incidence of WT1 alteration
- Recurrent mutations in key regulators of RA signaling (NSD1, SALL4, MED12)
- Some relapse are completely different from the diagnostic APL clone and derive from a pre leukemic clone.

Thanks

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