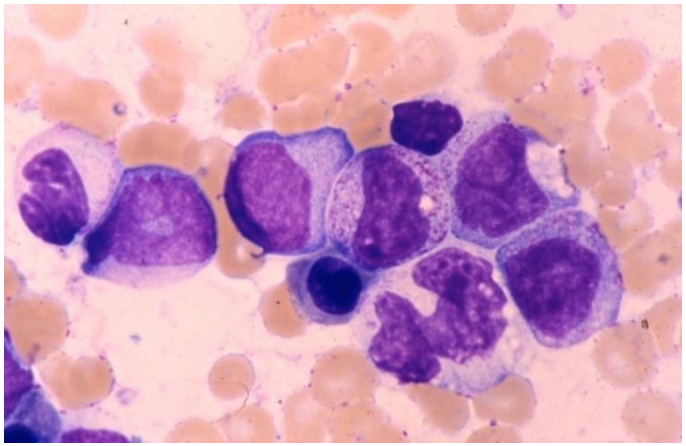
Transforming Mutations in Myeloid Leukaemia of Down Syndrome



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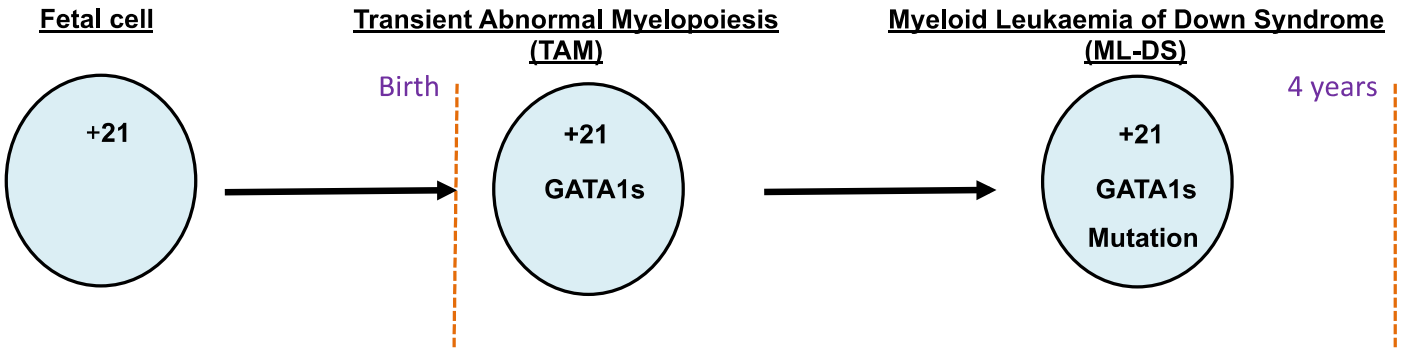
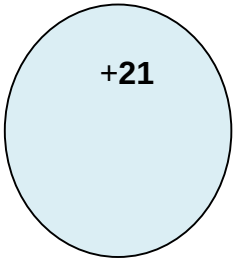
Multistep Leukaemogenesis: Co-operating mutations in cancer

- Cancer is a genetically complex disease. Often caused by step-wise acquisition of somatic mutations
- Understanding the function and co-operativity of these mutations is key to cancer biology and therapeutics.
- Blood cancers, such as Acute Myeloid Leukaemia, often simpler than solid tumours
- **Myeloid Leukaemia of Down Syndrome (ML-DS)**: a model for multistep leukaemogenesis

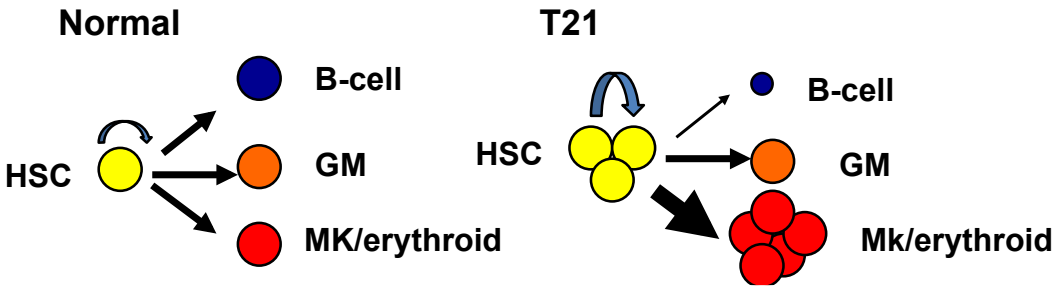


Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis

Fetal cell

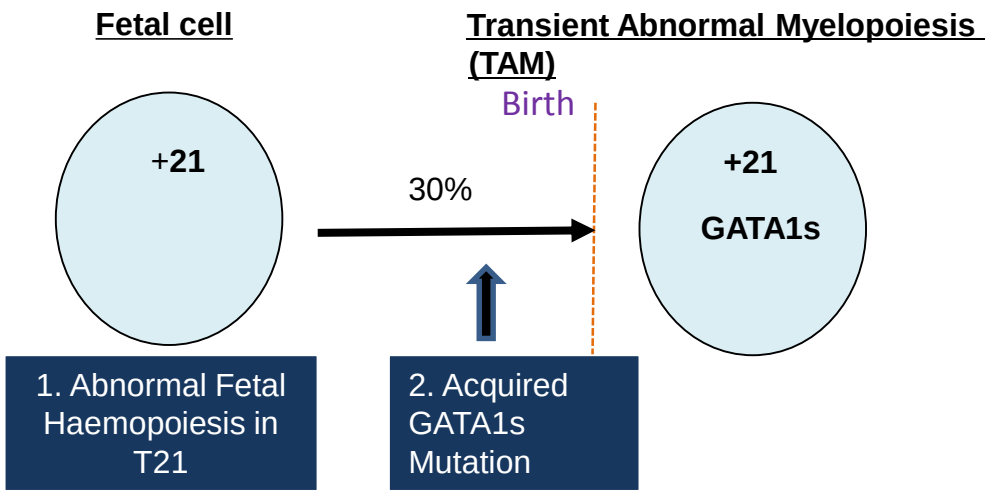


1. Abnormal Fetal Haemopoiesis in T21



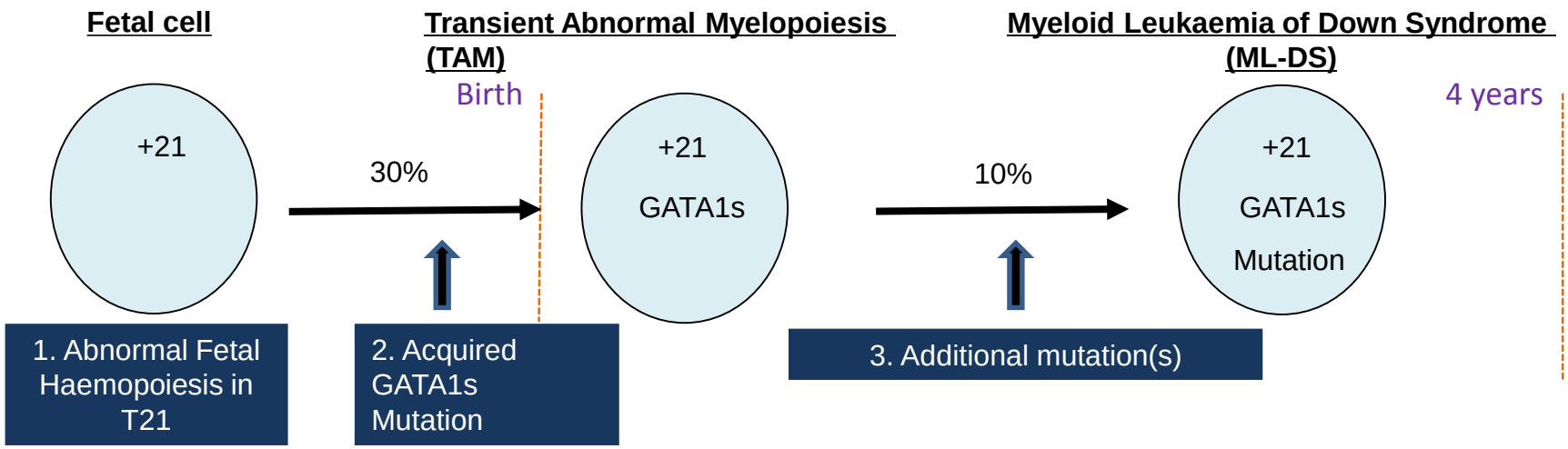
Roy et al., 2012 PNAS

Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis



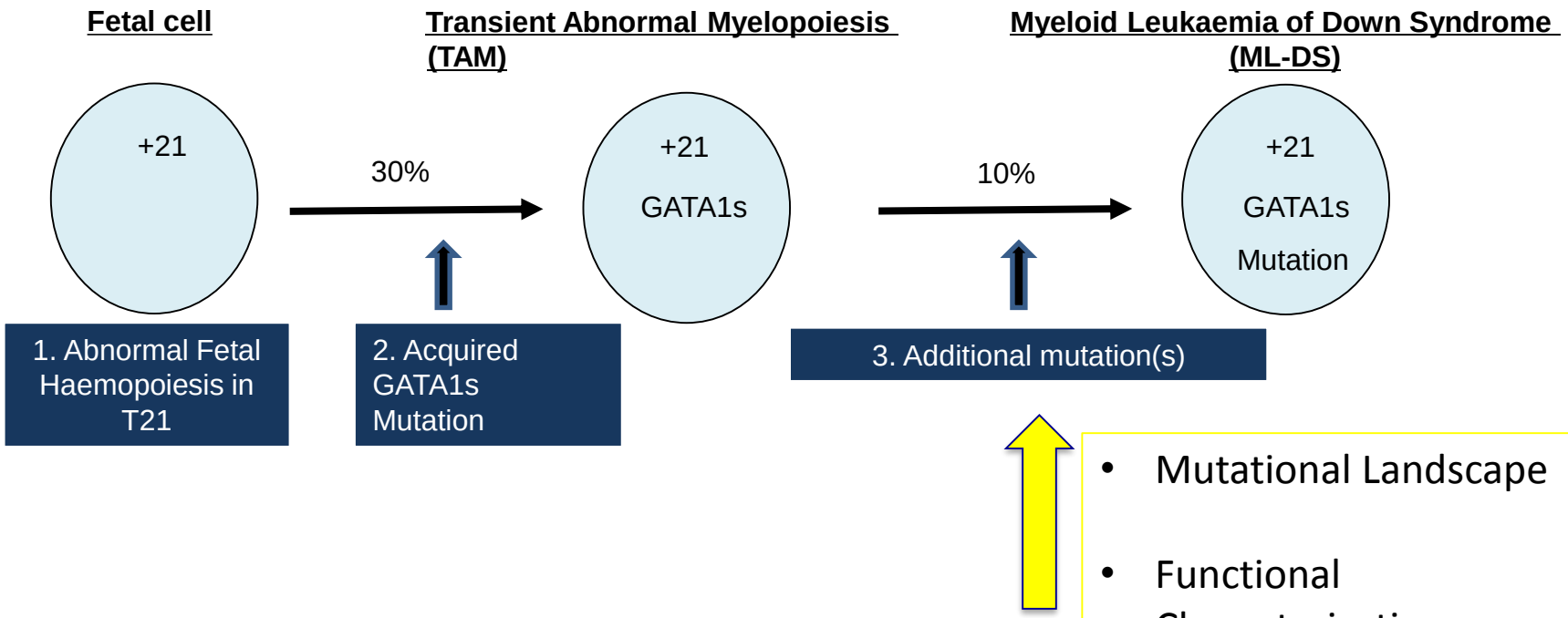
Alford et al., 2011 Blood
Roberts et al., 2013 Blood

Myeloid Leukaemia of Down Syndrome (ML-DS): a model for multistep leukaemogenesis



Yoshida et al., 2013 Nature Genetics
Nikolaev et al., 2013 Blood
Labuhn, Perkins et al., Cancer Cell 11-07-2019

Transforming mutations in Myeloid Leukaemia of Down Syndrome

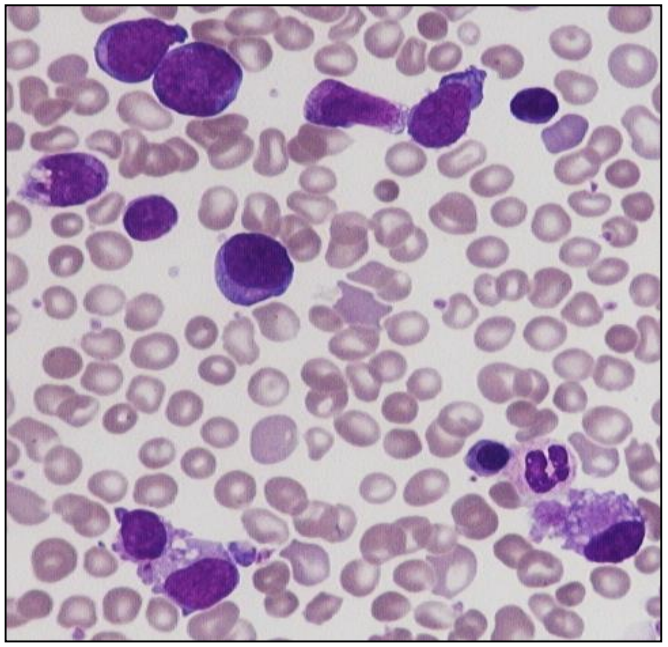


- Mutational Landscape
- Functional Characterisation
- Mechanism of cooperation

Labuhn, Perkins et al., Cancer Cell 11-07-2019

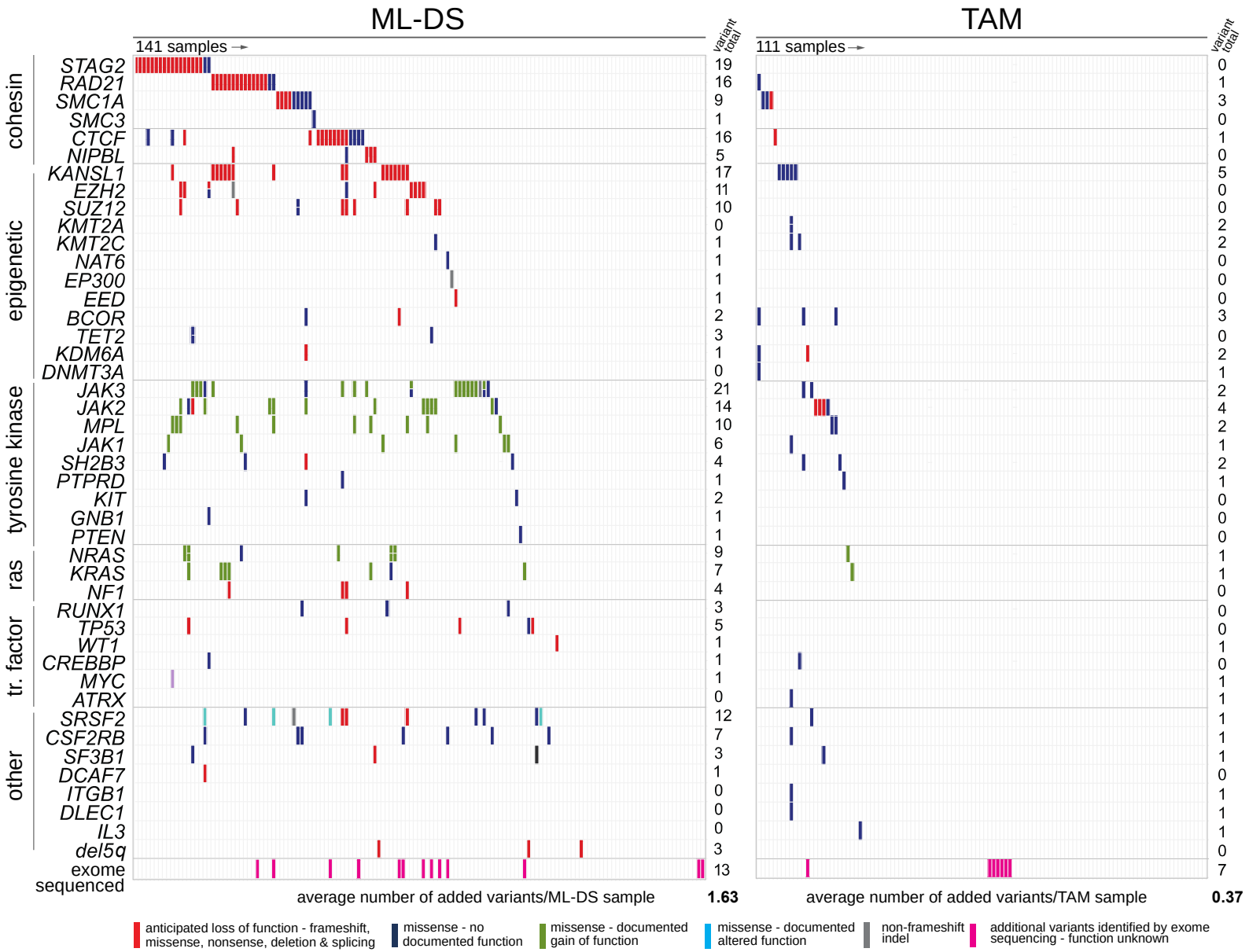
Transforming Mutations in ML-DS:

- Blood and BM samples
  - 111 TAM
  - 141 ML-DS samples
- 12 matched TAM and ML-DS pairs
- 20 samples exome sequenced
- Targeted resequencing (baits at Sanger Centre and access array Vyas lab)



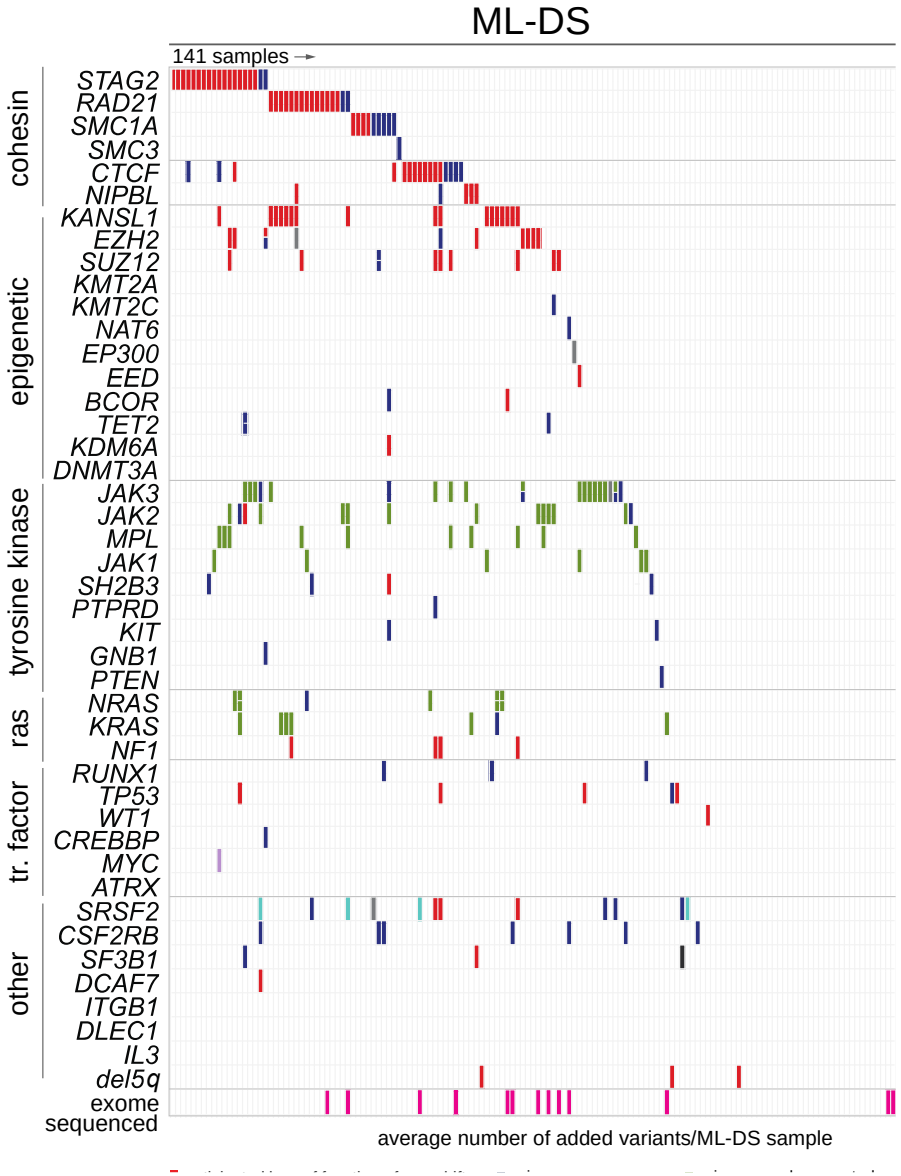
Labuhn, Perkins et al., Cancer Cell 11-07-2019

Transforming mutations in ML-DS



Labuhn, Perkins et al., Cancer Cell 11-07-2019

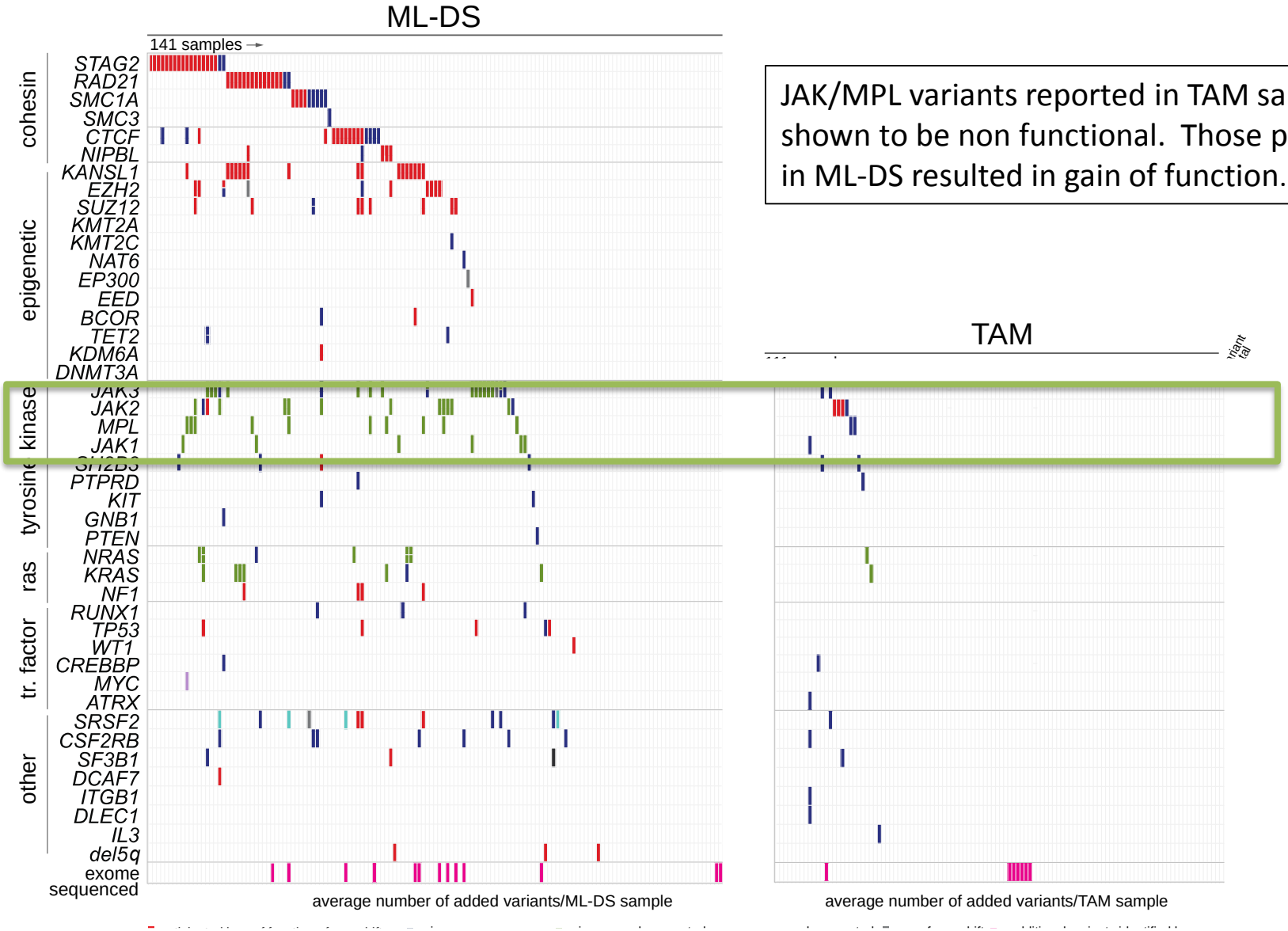
Transforming mutations in ML-DS



ML-DS enriched for additional somatic variants

Labuhn, Perkins et al., Cancer Cell 11-07-2019

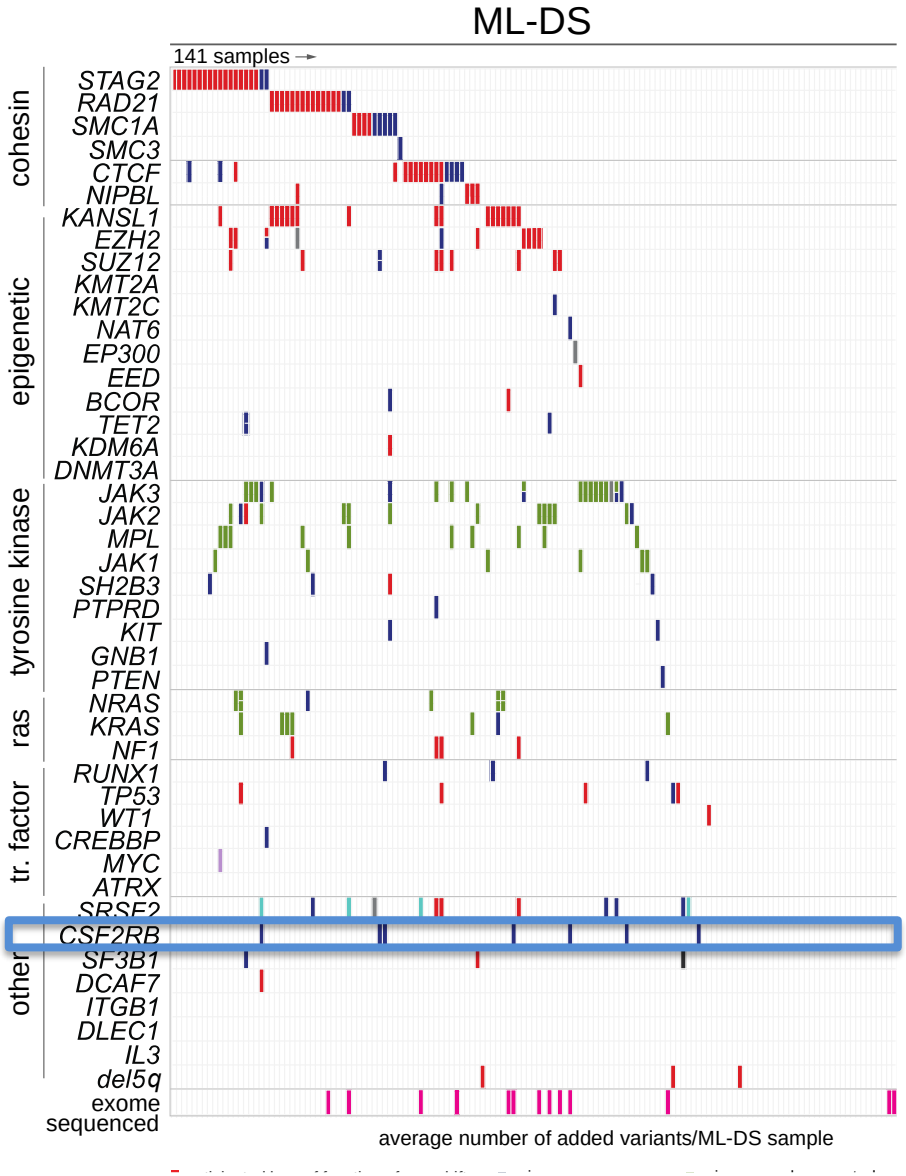
What is the functional significance of these variants?



JAK/MPL variants reported in TAM samples shown to be non functional. Those present in ML-DS resulted in gain of function.

Labuhn, Perkins et al., Cancer Cell 11-07-2019

What is the functional significance of these variants?

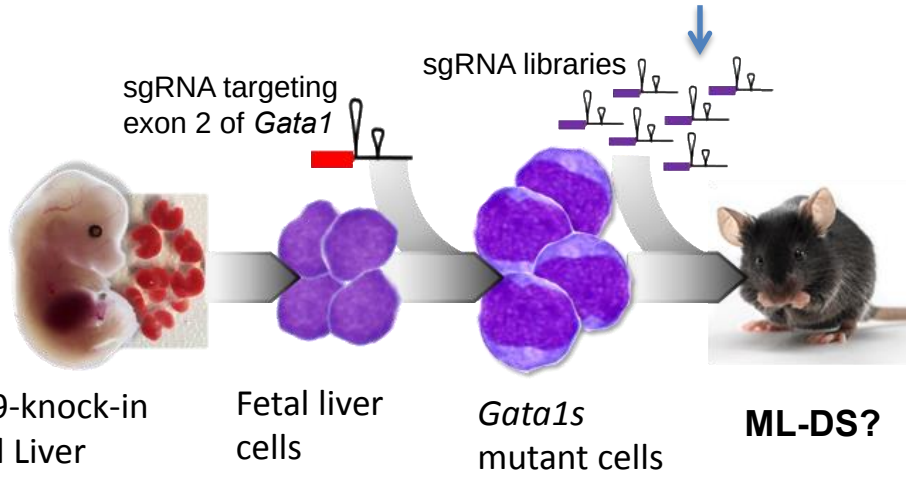


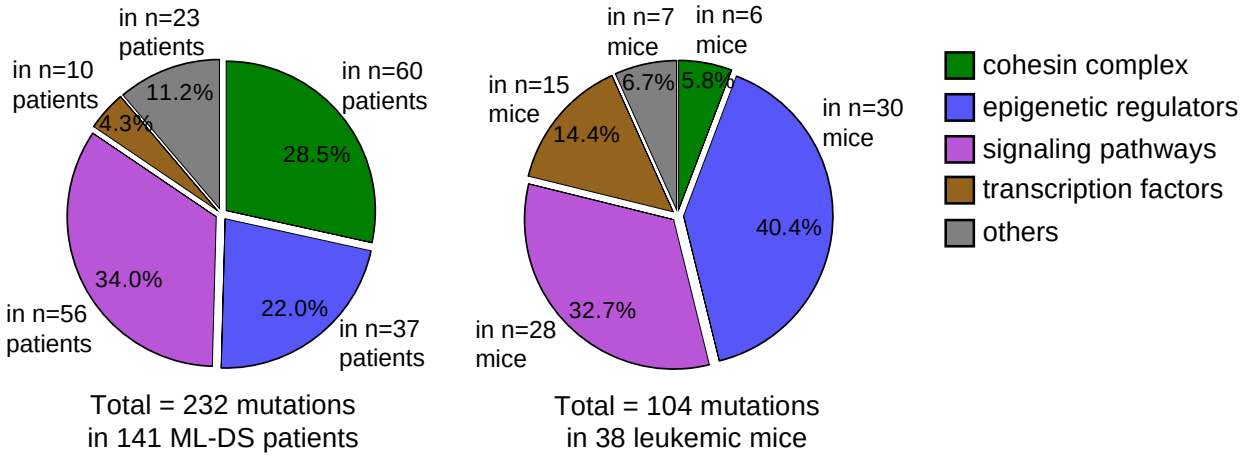
Identified novel hotspot in *CSF2RB*.
Functionally oncogenic.

Labuhn, Perkins et al., Cancer Cell 11-07-2019

Transforming mutations in ML-DS

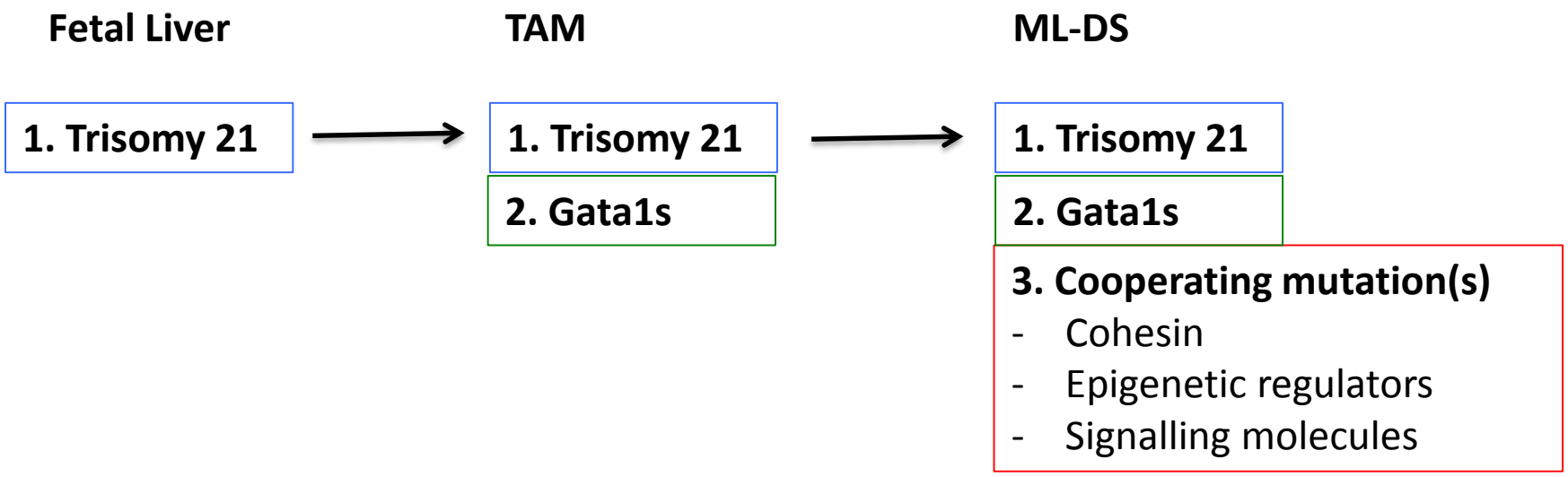
Multiplex in vivo loss of function screen



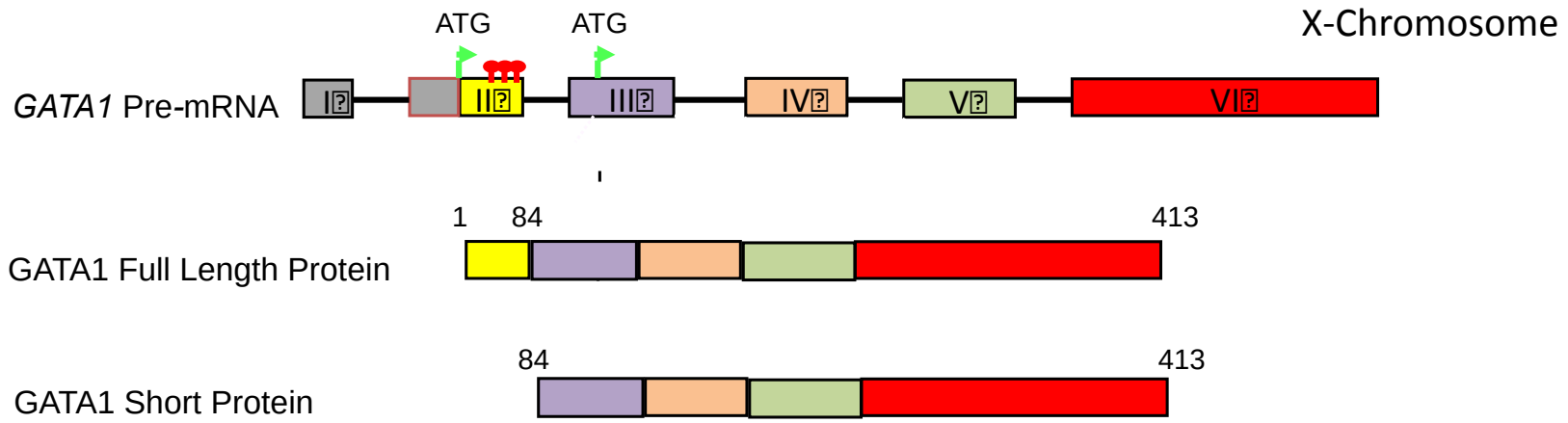


Labuhn, Perkins et al., Cancer Cell 11-07-2019

Co-operating mutations in ML-DS



GATA1s mutations in TAM and ML-DS

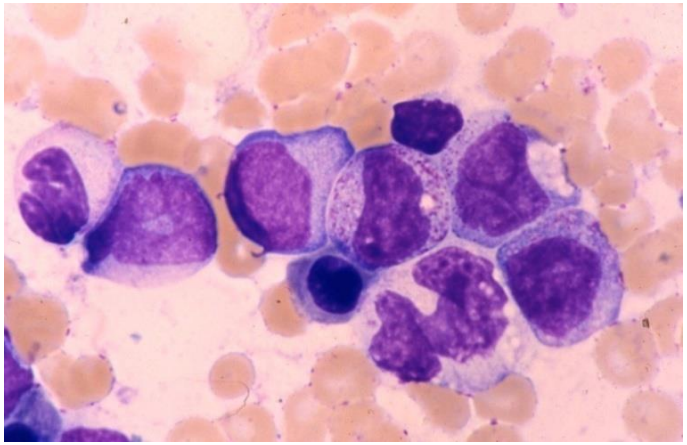


- Fetally acquired
- Exclusive production of GATA1s
- Uniform (exon 2/3)
- Necessary for development of TAM
- Not leukaemogenic in the absence of trisomy 21
- Disappear with resolution of TAM/ML-DS clone

Alford et al. 2011 Blood
Roberts et al. 2013 Blood
Ahmed et al. 2004 Blood
Hollanda et al. 2005 Nature Genetics

Conclusions

- Understanding mutational cooperativity is complex
- Cancer may result from multiple subtle effects coming together in a cell or population of cells to together cause proliferation and differentiation block
- Ongoing questions
  - Why are Gata1s mutations so common in DS?
  - Why is ML-DS enriched for cohesin gene mutations?
  - What is the role of T21?



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