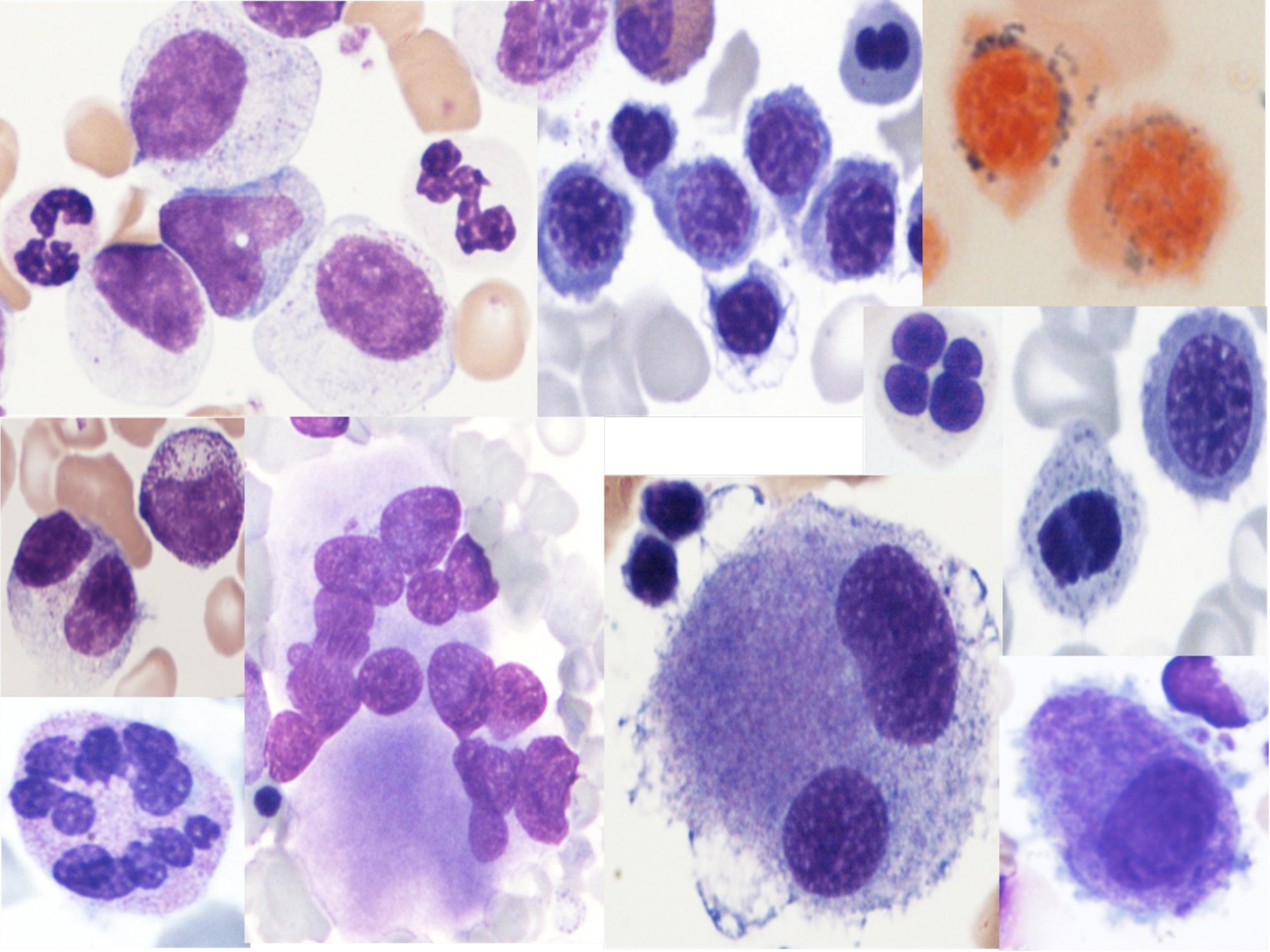
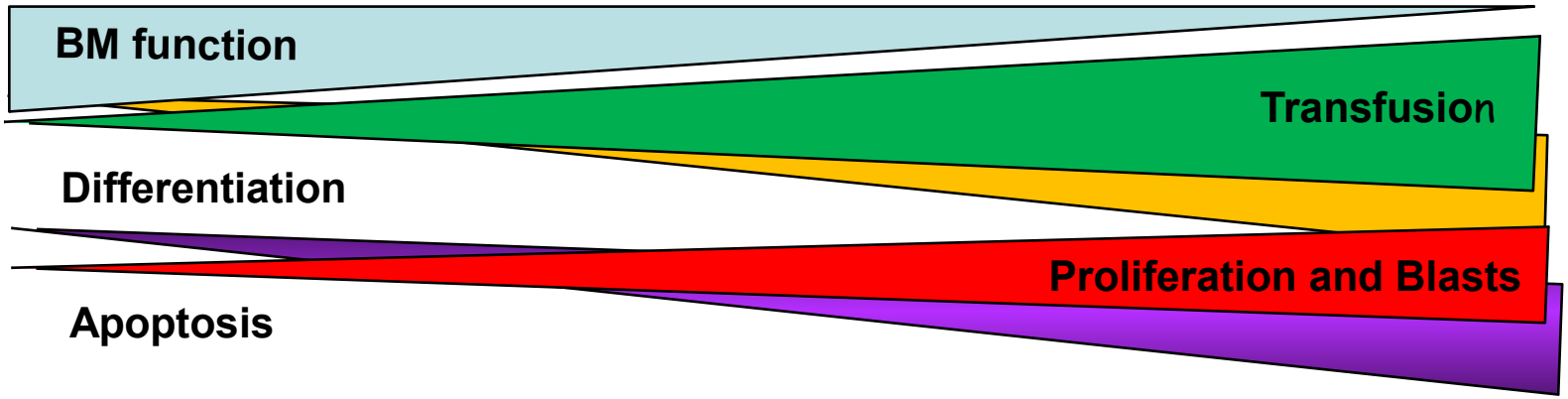
Genetic changes in MDS

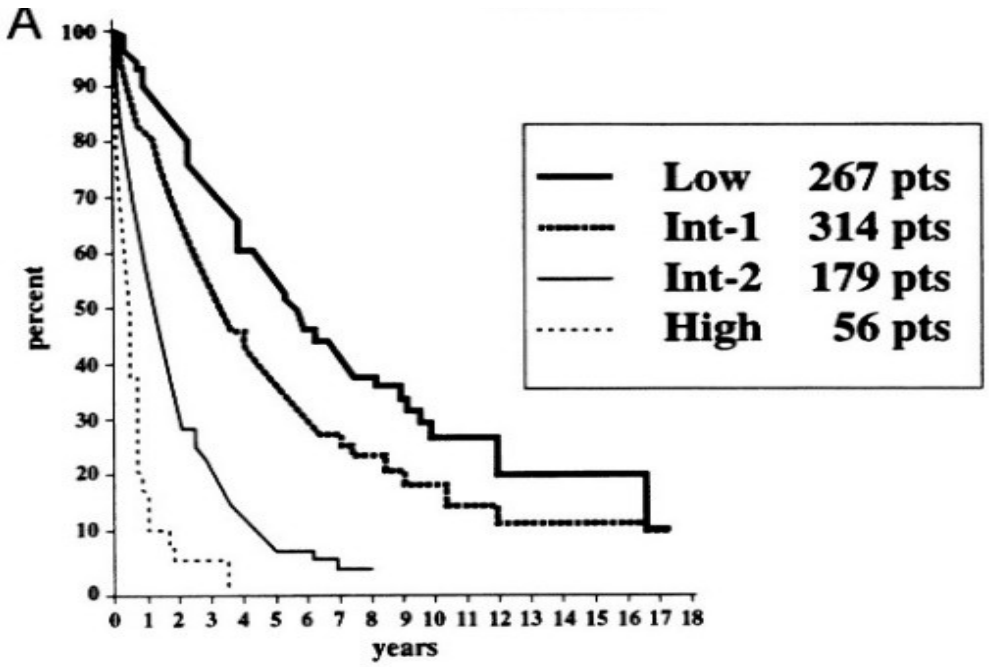


Spectrum of MDS

Asymptomatic,IPSS low **Symptomatic,IPSS Int-2/High Risk**

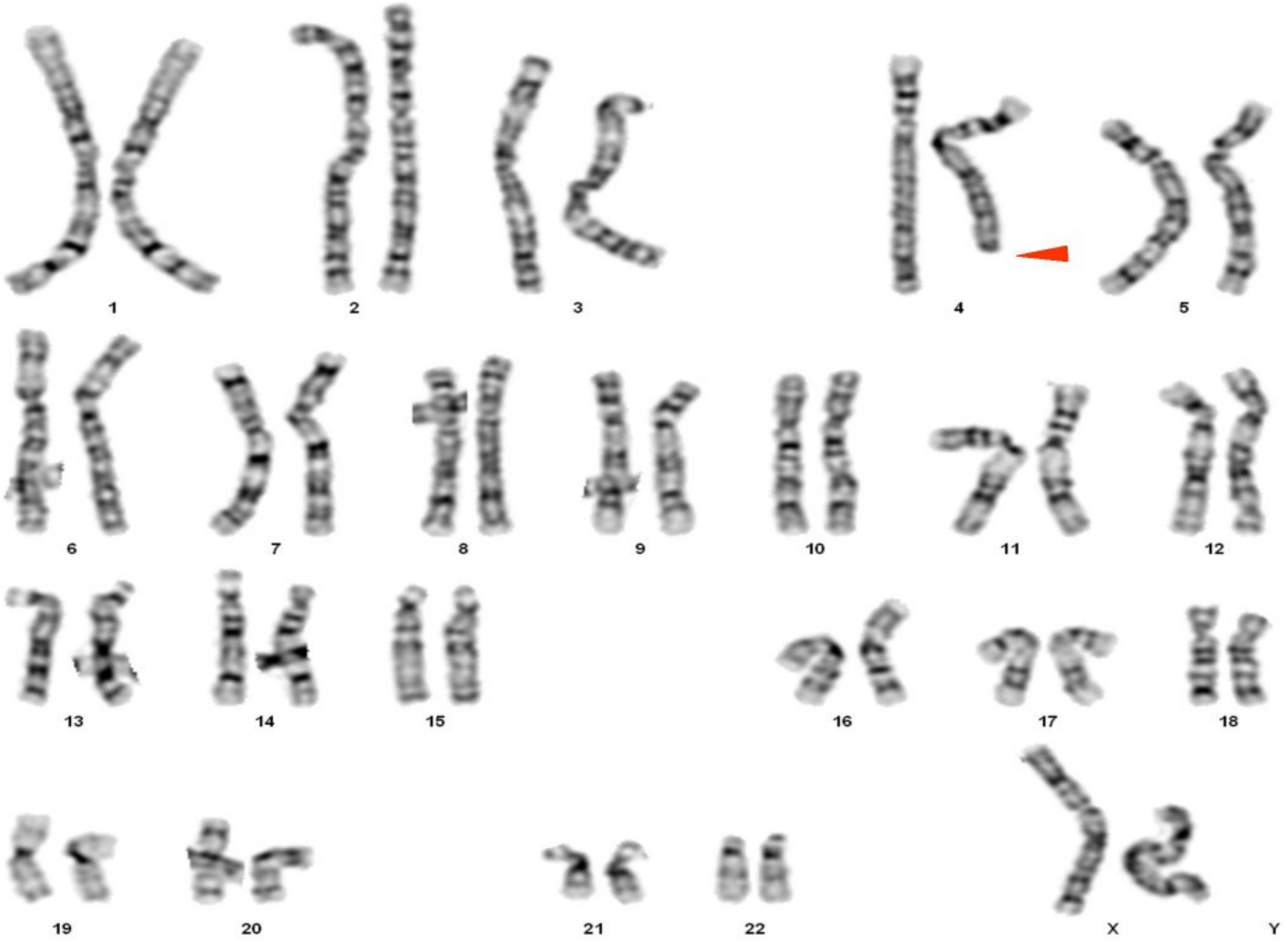


IPSS

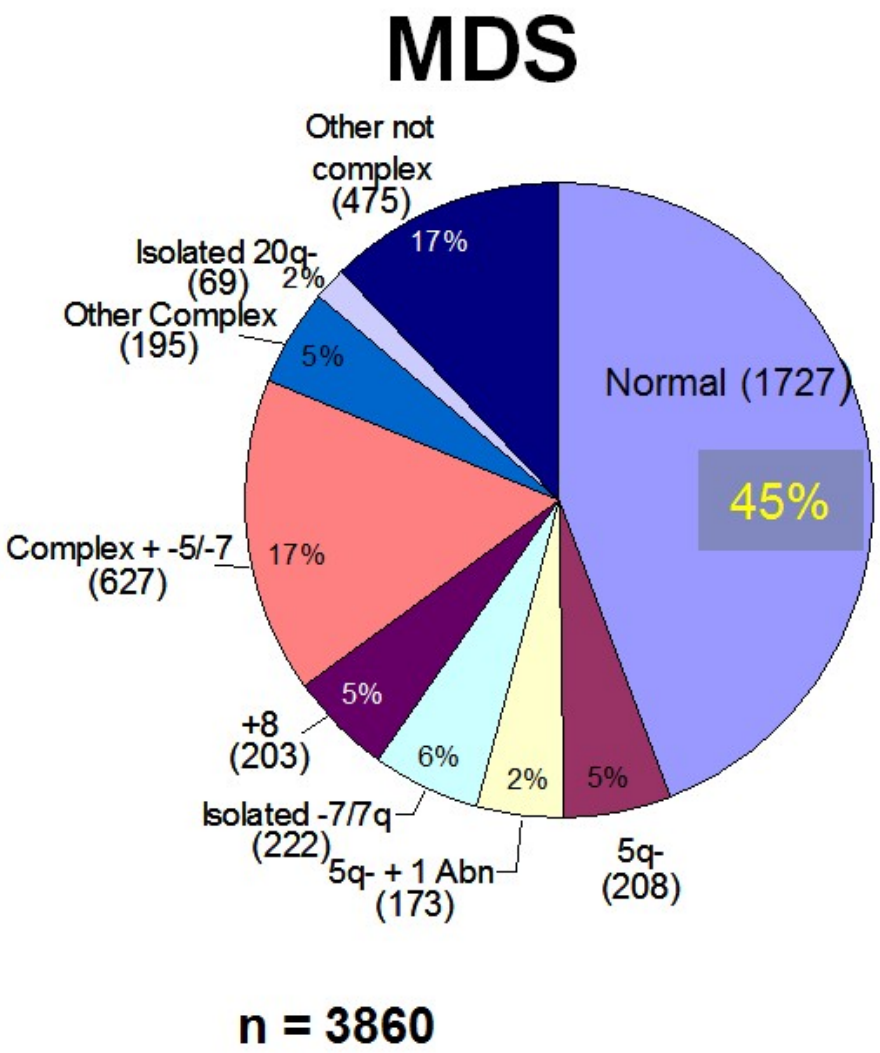


Greenberg, Blood 1997, Malcovati,JCO 2009,Greenberg Blood 2012

Gross genomic changes are detected by cytogenetics



MDS cytogenetic studies



Haase D. et al 2007

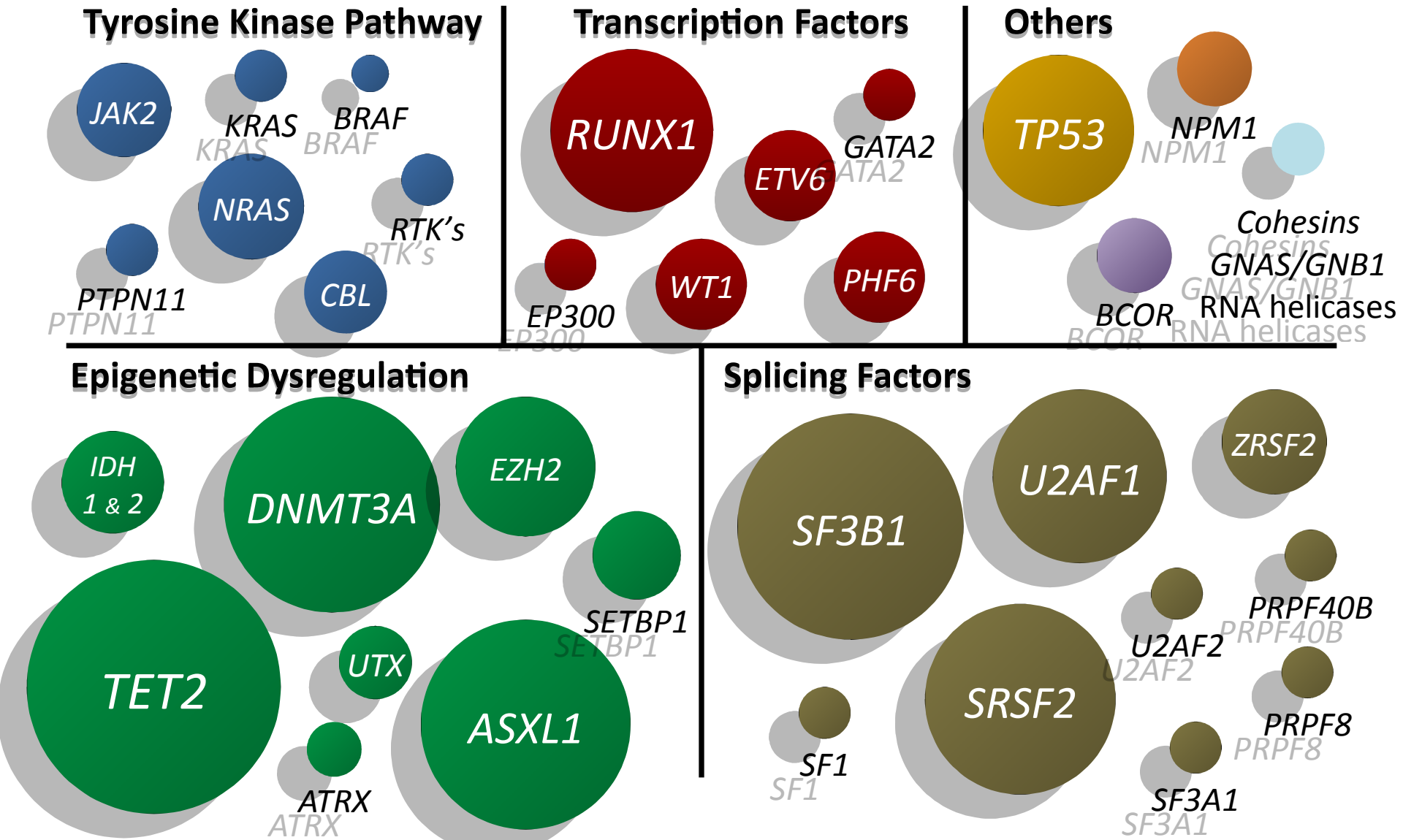
Mutations alter proteins

Small genetic changes can only be detected at the molecular level.

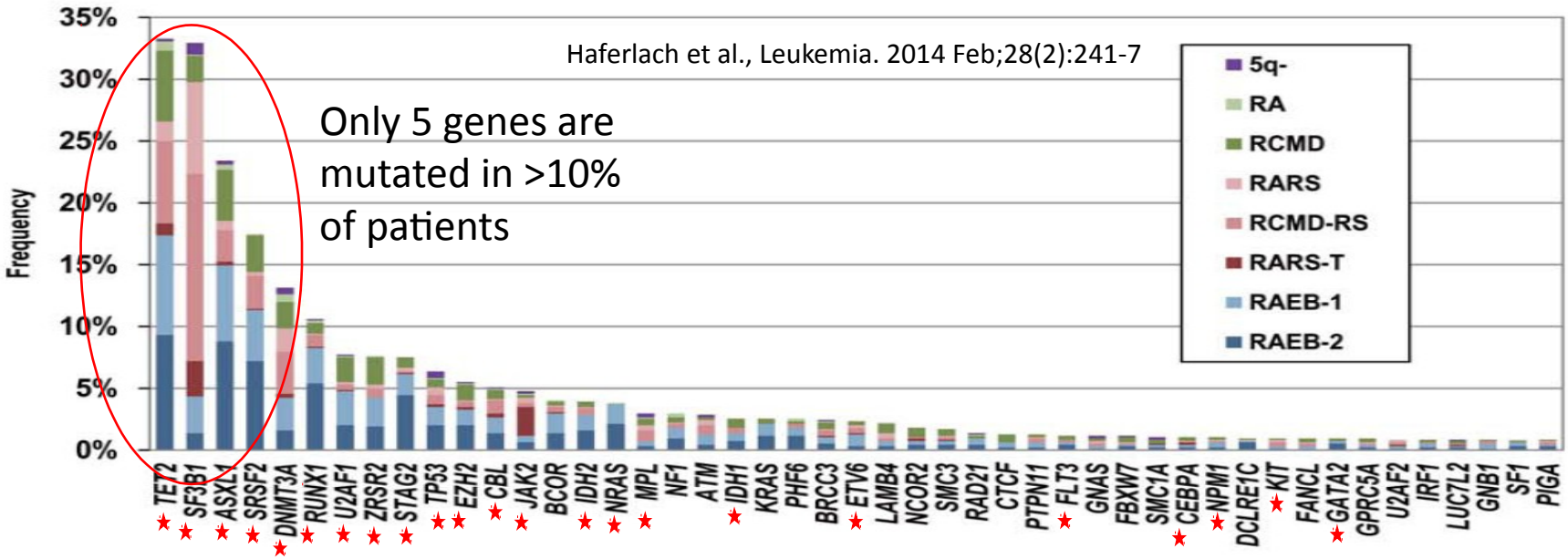
```
Met Lys Leu His His Trp Lys Phe Asp  *
ATG AAG TTA CAT CAT TGG AAA TTT GAT TGA
```

```
ATG AAG TTA CAT GAT TGA AAA TTT GAT TGA
Met Lys Leu His Asp  *  Lys Phe Asp  *
```

Point Mutations in MDS



Many mutations are very rare



★ Target present on the KCH panel

KCH: Myeloid Gene Panel (MGP)

24 genes mutations panel:

Transcription factors and cell cycle regulators

RUNX1

TP53
GATA2
ETV6
CEBPA
NPM1

Spliceosome component

SF3B1
U2AF1
SRSF2
ZRSR2

Epigenetic modifications

TET2
IDH1
IDH2
DNMT3A
KDM6A
ASXL1
EZH2

Signaling

NRAS
KRAS
FLT3
CBL
JAK2
KIT

Cohesin complex

STAG2

Research use only: clinical importance is yet to be determined

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Haematological Malignancy Diagnostic Centre

The challenge for the laboratory

- **Integrating genomic analysis into diagnostic, prognostic and therapeutic systems for patients.**

Therapy response / outcome

Lenalidomide (Revlimid)

TP53^{mut} do not achieve complete cytogenetic response in del5q MDS *(Jadersten JCO, Austin Kulasekararaj BJH)*

5'Azacytidine (Vidaza)

- *TET2*^{mut} may respond better
- *TET2*^{mut} and *DNMT3A*^{mut} may respond better
- *ASXL1* and *SF3B1* status also modulate response

Finally

- Genetic testing is more widely available:
  - Cheaper, simpler, faster
- Mutations help in the certainty of diagnosis.
- Incorporation into prognostic models such as IPSS
- The era of biomarker-based therapy may not be too distant

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