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Pediatric MDS with a germline *GATA2* heterozygous deletion, monosomy 7, and somatic *CRLF2* mutation

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Clinical History

12 year old male, previously healthy, presented with fever, cough, and diagnosed with pneumonia.

CBC: WBC 1.9 K/uL, Hgb 9.4 g/dL, Hct 27.3%, RBC 2.77 M/uL, MCV 98.6 fL, MCH 33.9 pg, MCHC 34.4 g/dL, RDWCV 15.3%, plt 409 K/uL, ANC 0.79 K/uL, **AMC 0.11 K/uL**, **ALC 0.93 K/uL** and 1.6% blasts.

Fig 2: At diagnosis, bone marrow aspirates with dysplastic megakaryocytes.

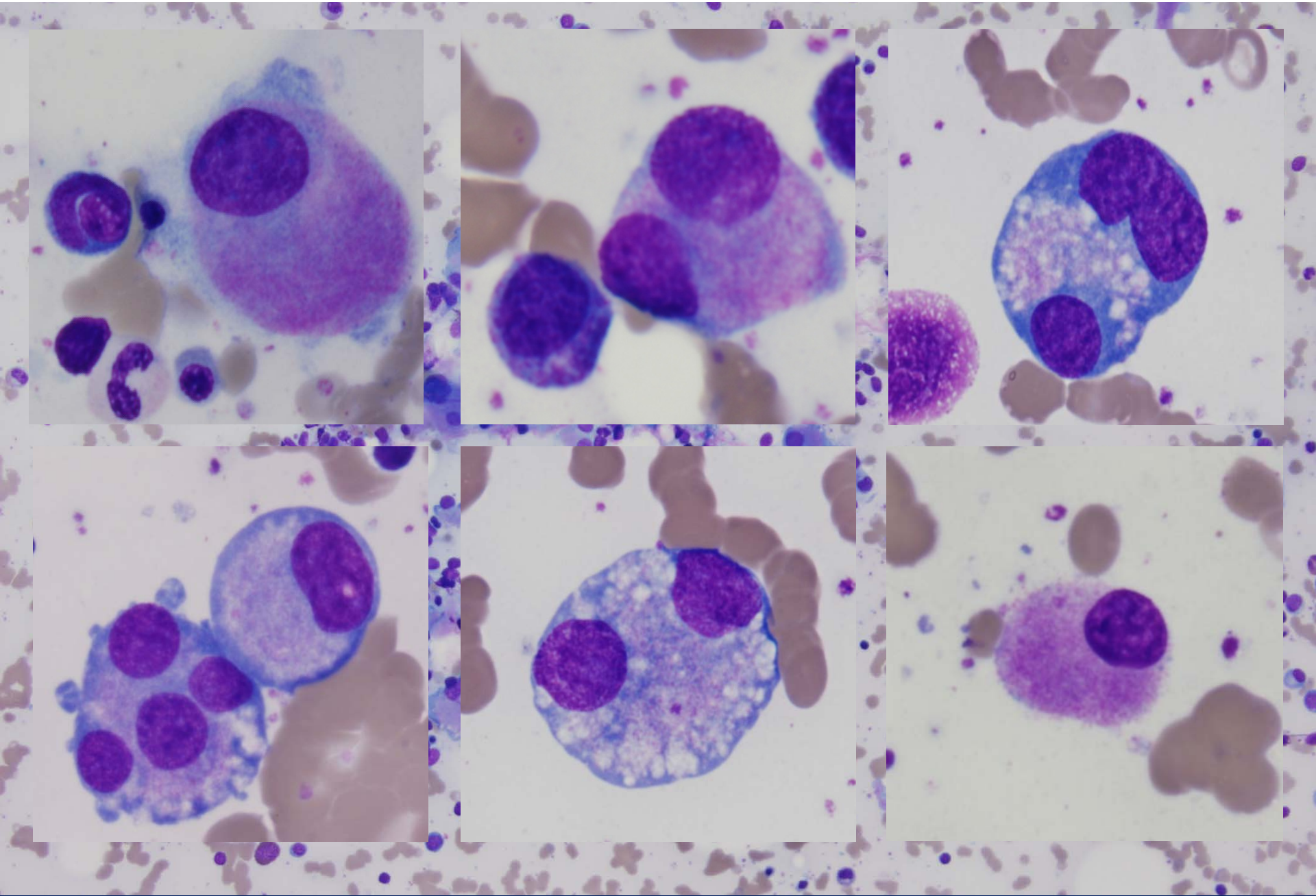
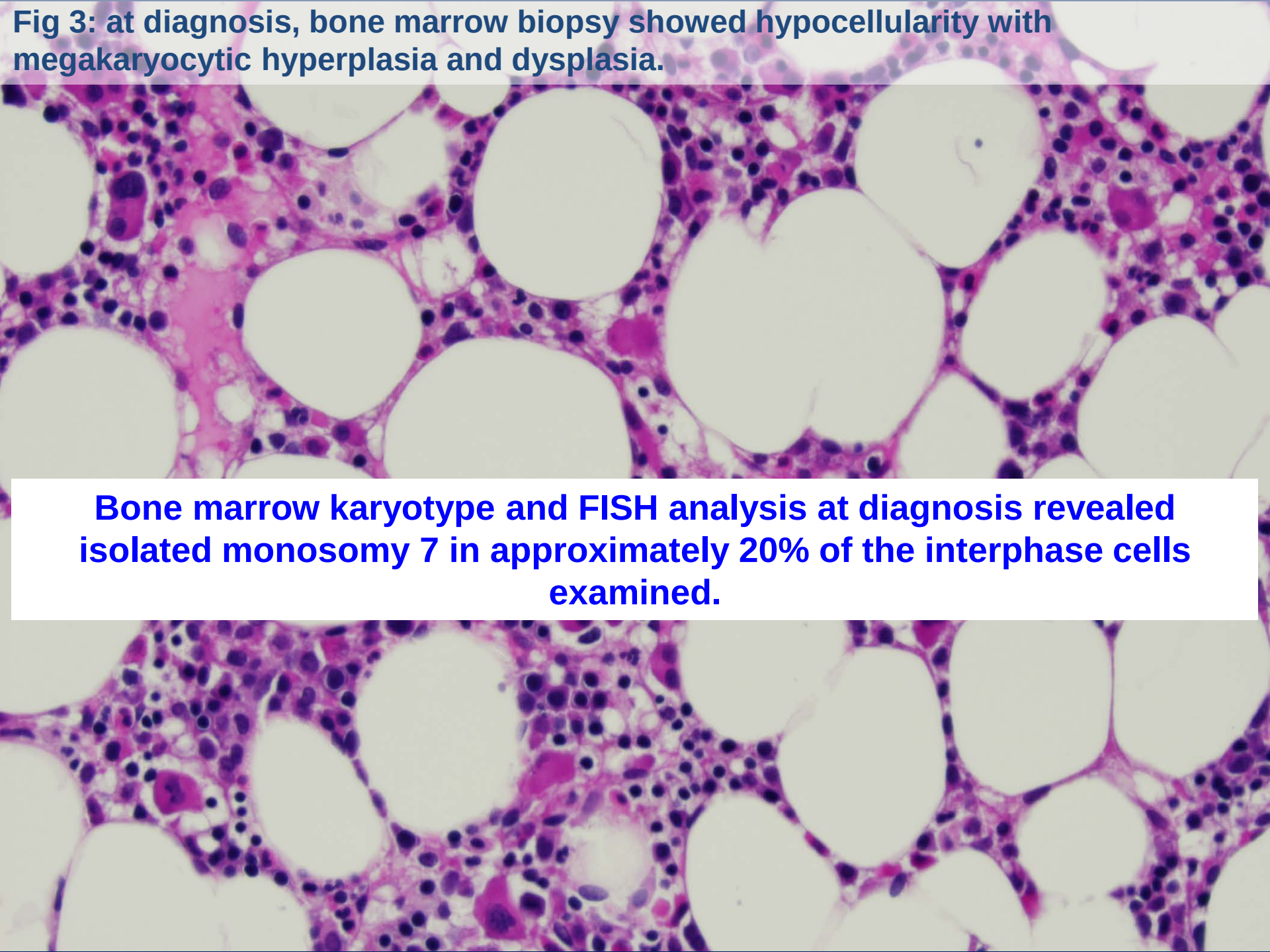
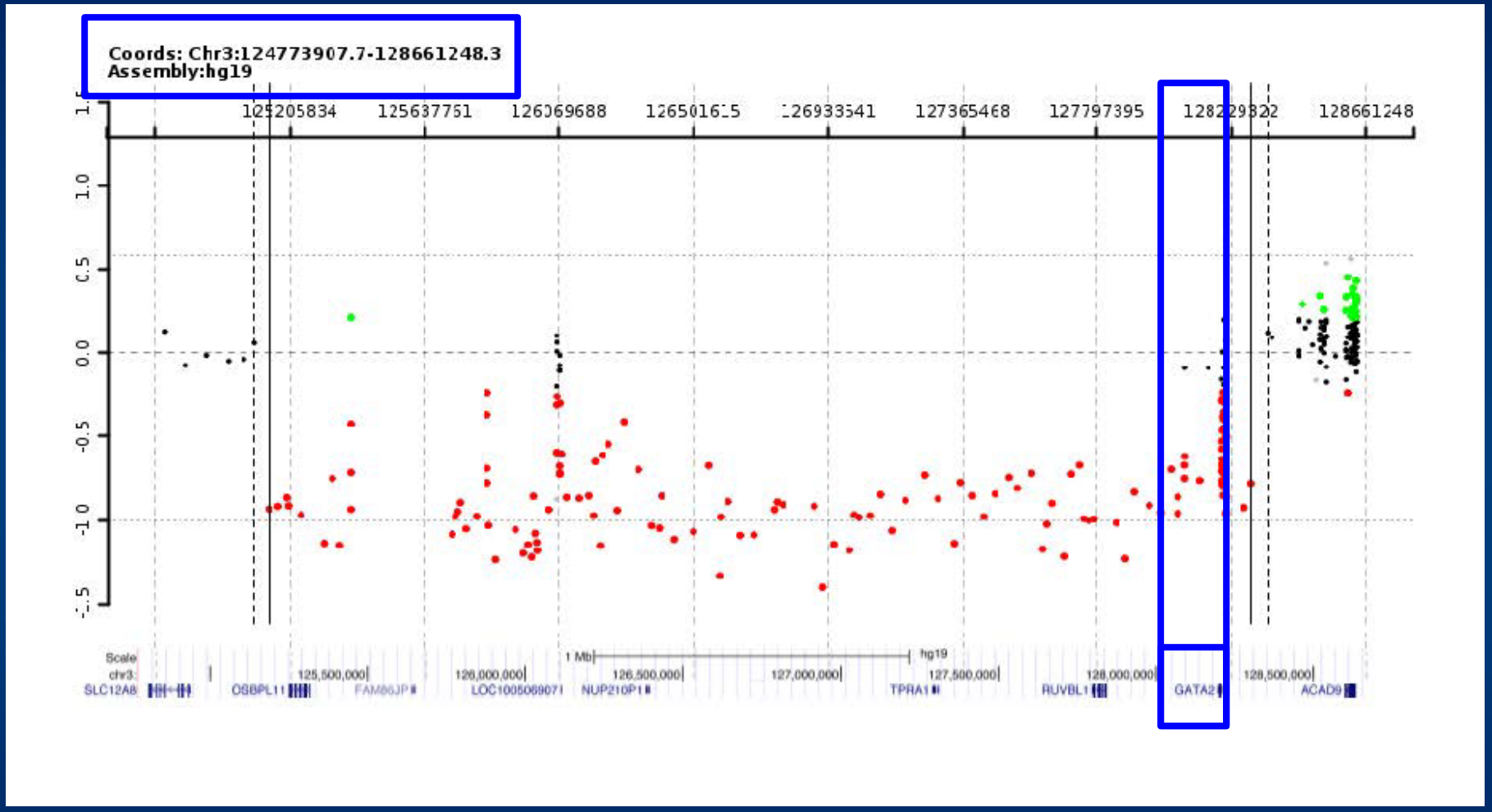


Fig 3: at diagnosis, bone marrow biopsy showed hypocellularity with megakaryocytic hyperplasia and dysplasia.



Bone marrow karyotype and FISH analysis at diagnosis revealed isolated monosomy 7 in approximately 20% of the interphase cells examined.

Fig 4: (at diagnosis) array CGH showed heterozygous deletion encompassing GATA2.



Familial testing for *GATA2* mutations revealed no mutations in both parents.

Discussion Points

1. *GATA2*-related spectrum disorders with emphasis on pediatric MDS
2. Molecular detection for germline *GATA2* mutation in pediatric MDS
3. Role of identification of somatic mutations

Role of GATA2 in hematopoiesis

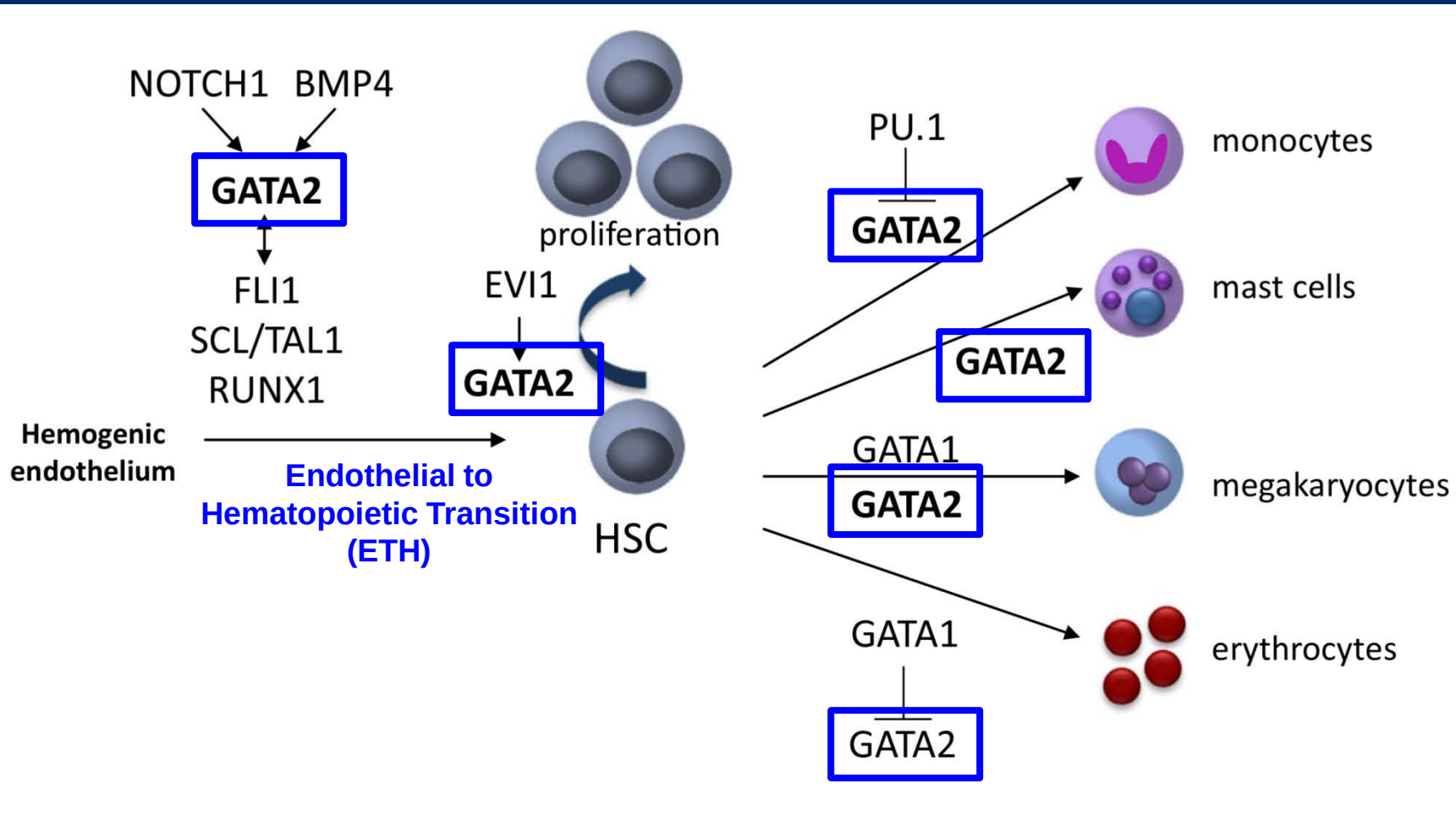
The *GATA2* gene encodes a chief hematopoietic transcription factor.

Through its 2 zinc finger domains (ZFs) can occupy GATA DNA motifs in several thousand genes.

GATA2 plays a critical role in hematopoietic development [hemogenic endothelium to hematopoietic stem cells (HSC) transition, and required for HSC survival and self-renewal].

S. Hirabayashi et al. Heterogeneity of *GATA2*-related myeloid neoplasms. Int J Hematol (2017) 106: 175-182.

Role of GATA2 in hematopoiesis



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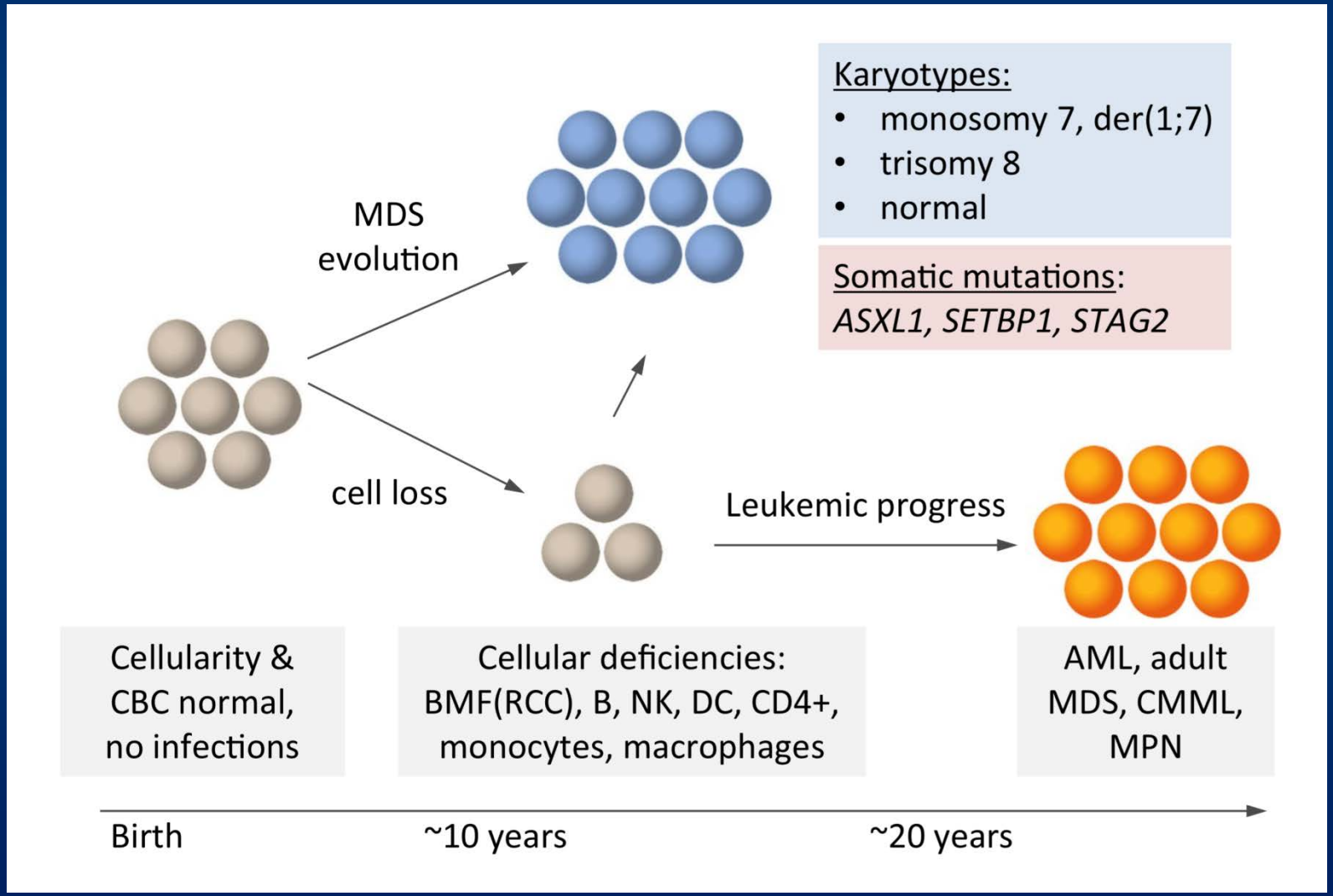
Phenotype of GATA2 deficiency

GATA2 germline mutations result in loss of the second ZF (ZF2) and haplo-insufficiency.

Hence the term GATA2 deficiency or haploinsufficiency widely accepted to describe GATA2-spectrum disorders.

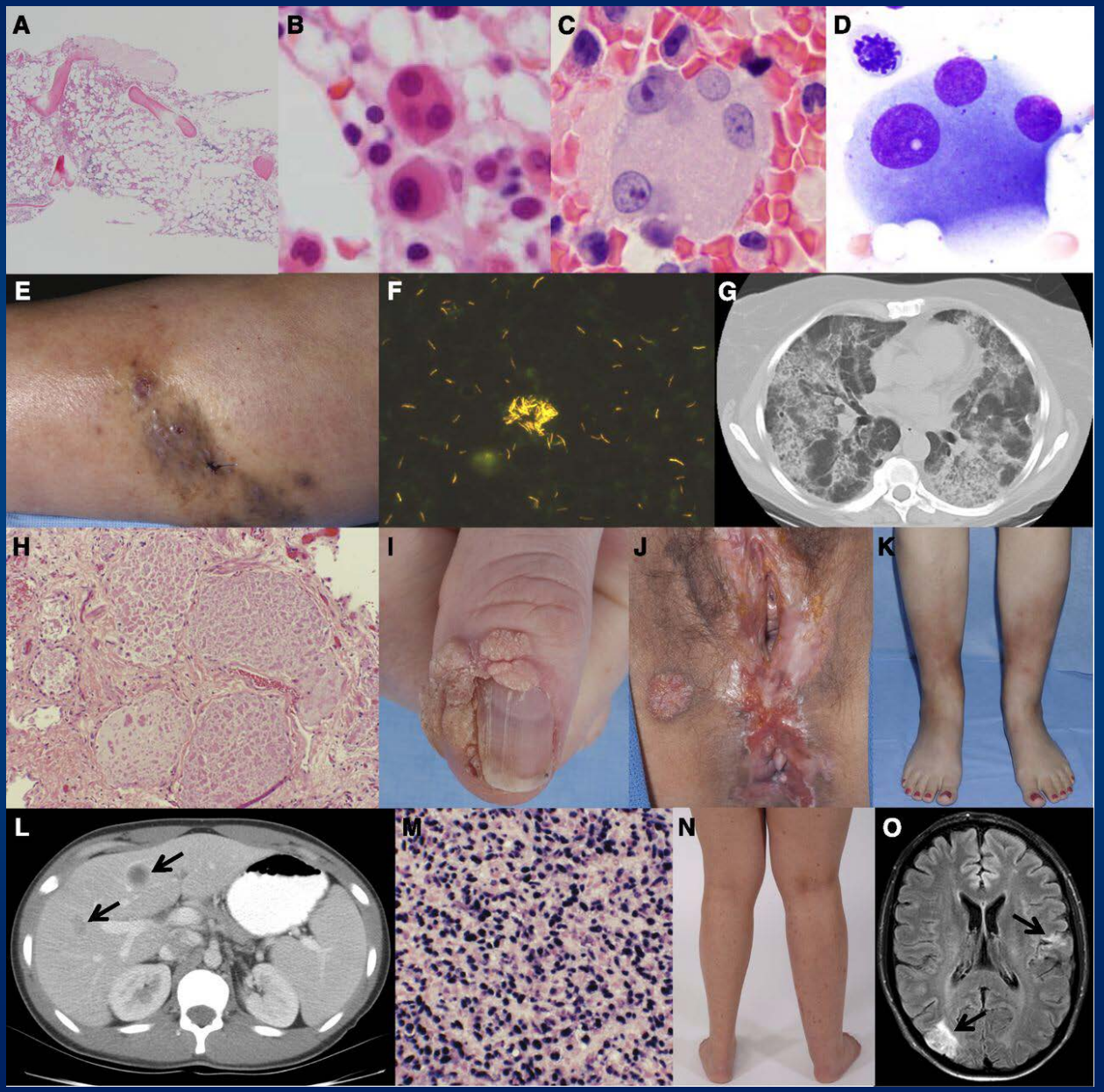
Evolution of MDS in GATA2 deficiency background



S. Hirabayashi et al. Int J Hematol (2017) 106: 175-182.

Phenotype of GATA2 deficiency

- Familial MDS/AML
- Pediatric MDS
- MonoMac syndrome/DCML deficiency
- Pulmonary alveolar proteinosis
- Emberger syndrome
- CMML/JMML
- Aplastic anemia
- Chronic neutropenia



MA Spinner et al. Blood 2014; 123(6): 809-821

GATA2-related Pediatric MDS

EWOG-MDS studies of 426 with primary pediatric MDS and 82 of secondary MDS

Germline *GATA2* mutations account for 15% of advanced and 7% of all primary pediatric MDS; versus <1% in adult MDS.

72% of adolescents with MDS and monosomy 7 harbor a germline mutation in *GATA2.*

~70% of pediatric MDS occur sporadically without family history of hematologic malignancies.

GATA2 mutations were absent in secondary MDS (therapy-related or post aplastic anemia)

Wlodarski et al. *Blood*. 2016 Mar 17;127(11):1387-97

S. Hirabayashi et al. Heterogeneity of *GATA2*-related myeloid neoplasms. Int J Hematol (2017) 106: 175-182.

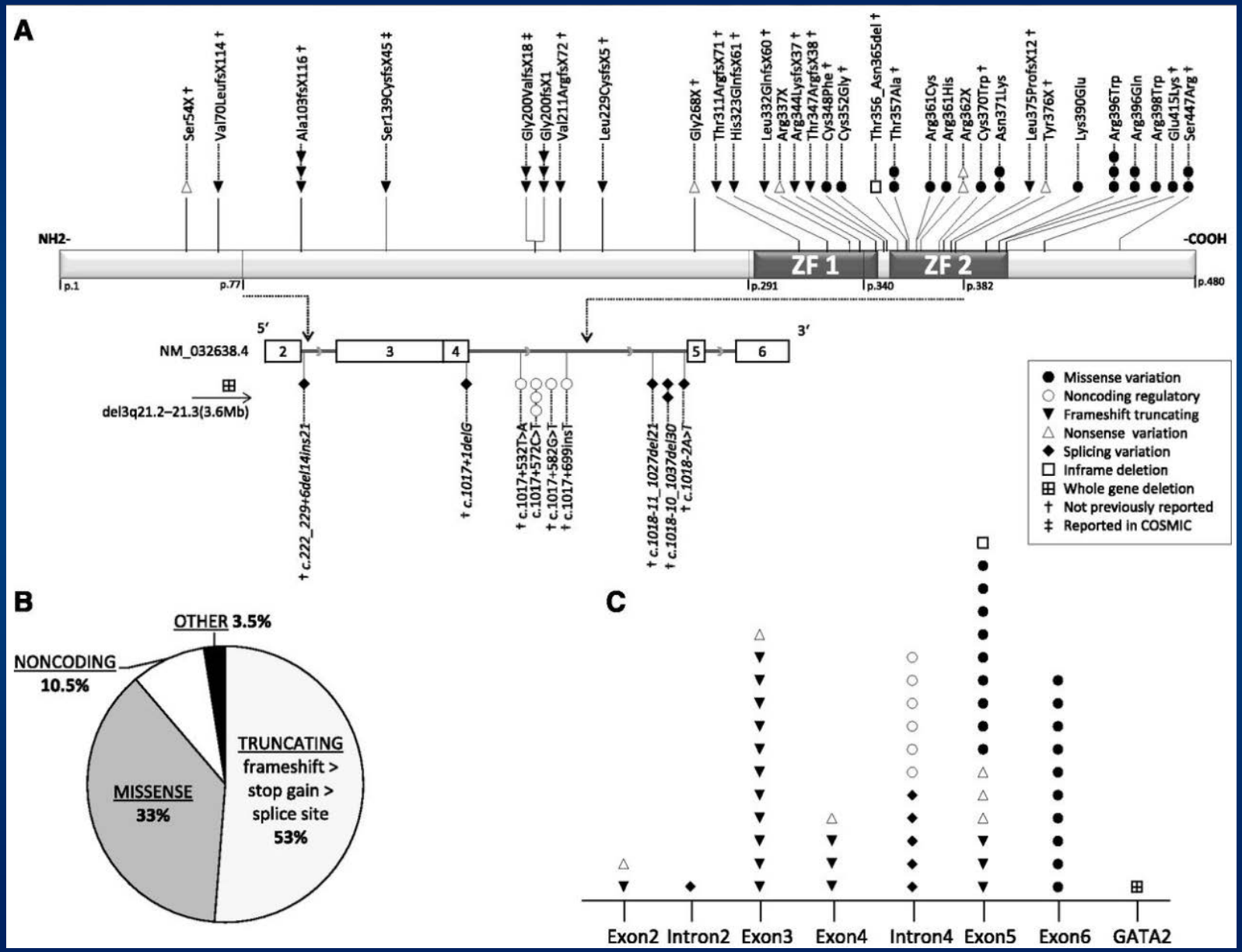
GATA2-related Pediatric MDS

GATA2 screening should be considered for all pediatric MDS with monosomy 7, trisomy 8, or in patients with non-hematologic features of GATA2 deficiency.

Interestingly, monocytopenia is not a consistent immunological feature in pediatric cohort, but rather B-lymphopenia.

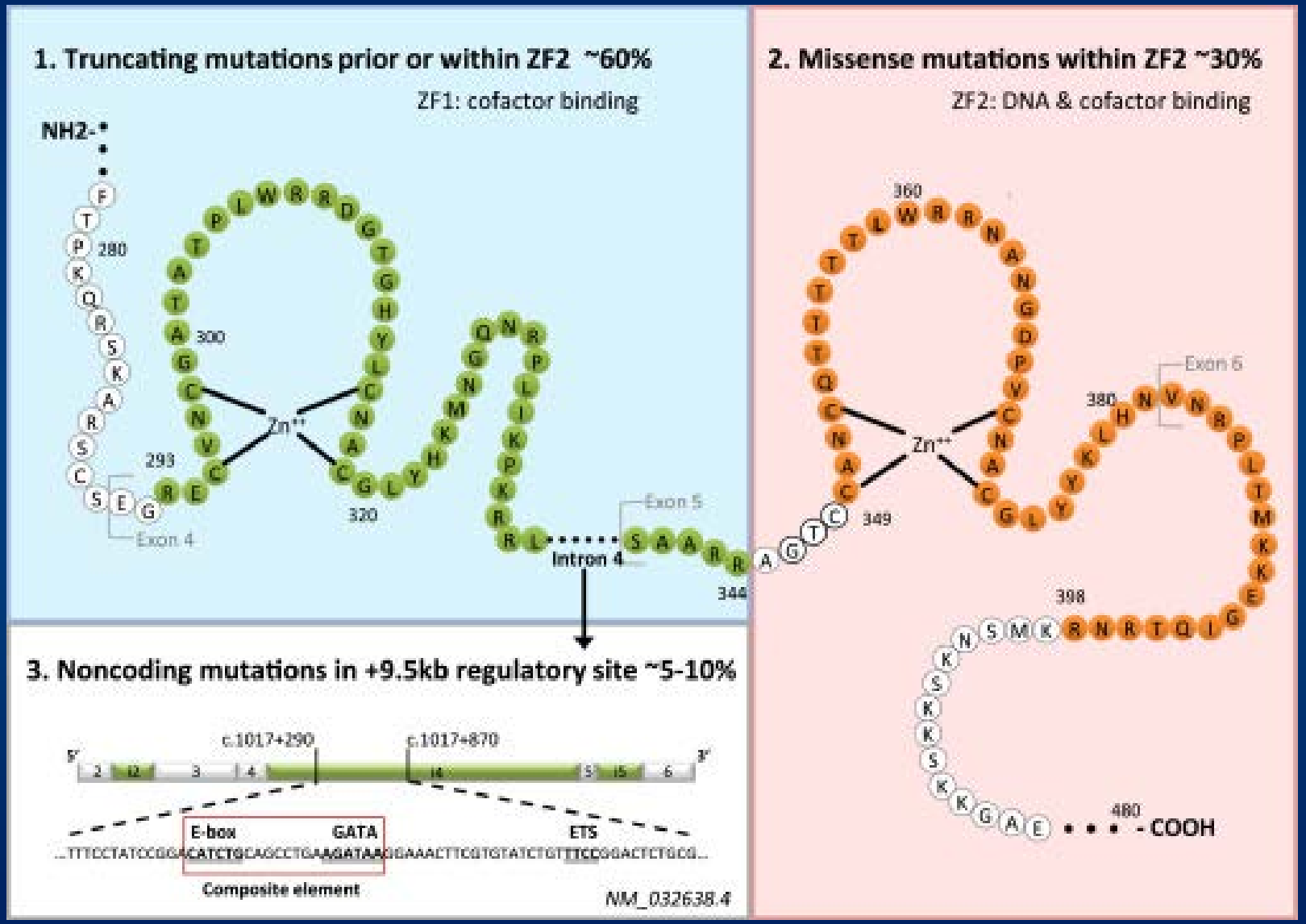
S. Hirabayashi et al. Heterogeneity of *GATA2*-related myeloid neoplasms. Int J Hematol (2017) 106: 175-182.

Spectrum of *GATA2* Mutations



Wlodarski et al. *Blood*. 2016 Mar 17;127(11):1387-97

Genetic causes of *GATA2* deficiency



Wlodarski MW et al. *Seminars in Hematology* May 2017

GATA2 germline mutation testing

Multimodal approach is needed to assess all potential *GATA2* mutations

- Mutations occur throughout the gene
- Whole exome sequencing will miss intronic variants and possibly whole gene deletions

Proposed diagnostic work up for suspected GATA2 deficiency

- Sanger- or NGS-base analysis of coding sequence, intron 4 enhancer
- Copy number analysis to rule out *GATA2* gene deletion

S. Hirabayashi et al. Heterogeneity of *GATA2*-related myeloid neoplasms. Int J Hematol (2017) 106: 175-182.

Role for acquired mutation testing?

Recent studies have investigated the potential role for acquired (somatic) mutation testing in *GATA2*-MDS patients

Somatic mutations may have potential prognostic effect in children with inherited *GATA2* mutations

ASXL1, *NRAS*, ***RUNX1***, ***SETBP1***,*TP53*, *WT1*, *IDH2*

Chiba K et al. *Haematologica*, Oct. 2015

RUNX1, ***SETBP1***, *IKZF1*, and *CRLF2*

Fisher KE et al., *Blood Advances* Feb. 2017

ASXL1, ***SETBP1*** (unpublished observations)

Wlodarski MW et al. *Seminars in Hematology* May 2017

Treatment & Future Directions

GATA2 mutations are not independently prognostic, but the high risk for cytogenetic evolution, cytopenias, and advanced disease warrant close monitoring

HSCT is recommended prior to the development of monosomy 7 and/or increasing blasts

More studies are needed to assess the impact of additional acquired somatic mutations on prognosis and clinical management

M. Wlodarski et al. GATA2 deficiency and related myeloid neoplasms. Semin Hematol (2017) 54(2): 81-86

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Proposed Diagnosis

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Pediatric MDS with a germline *GATA2* heterozygous deletion, monosomy 7, and somatic *CRLF2* mutation

Panel Diagnosis

Refractory Cytopenia of Childhood (RCC) with germline *GATA2* mutation

Thank You.

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Genetic causes of *GATA2* deficiency

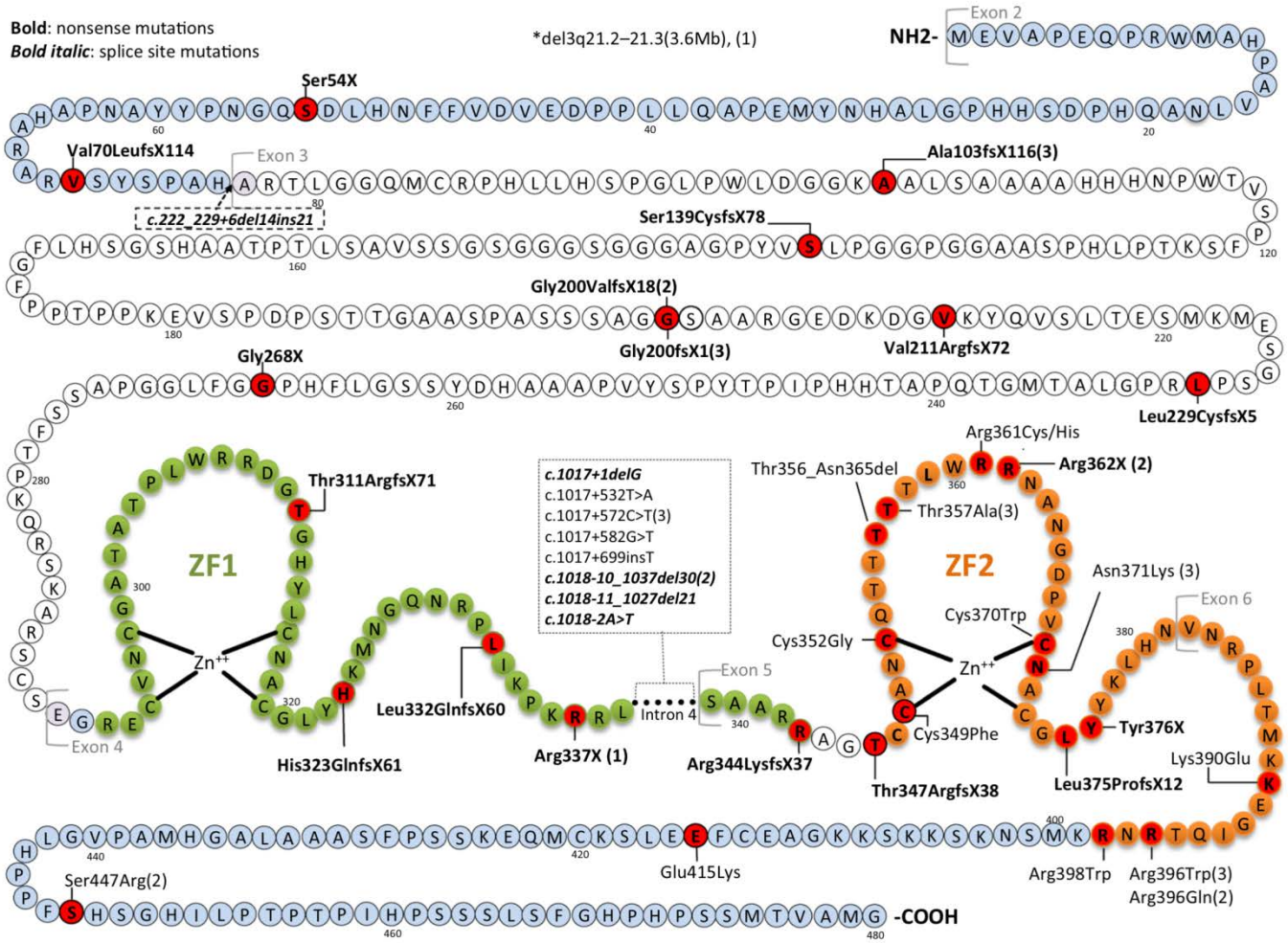
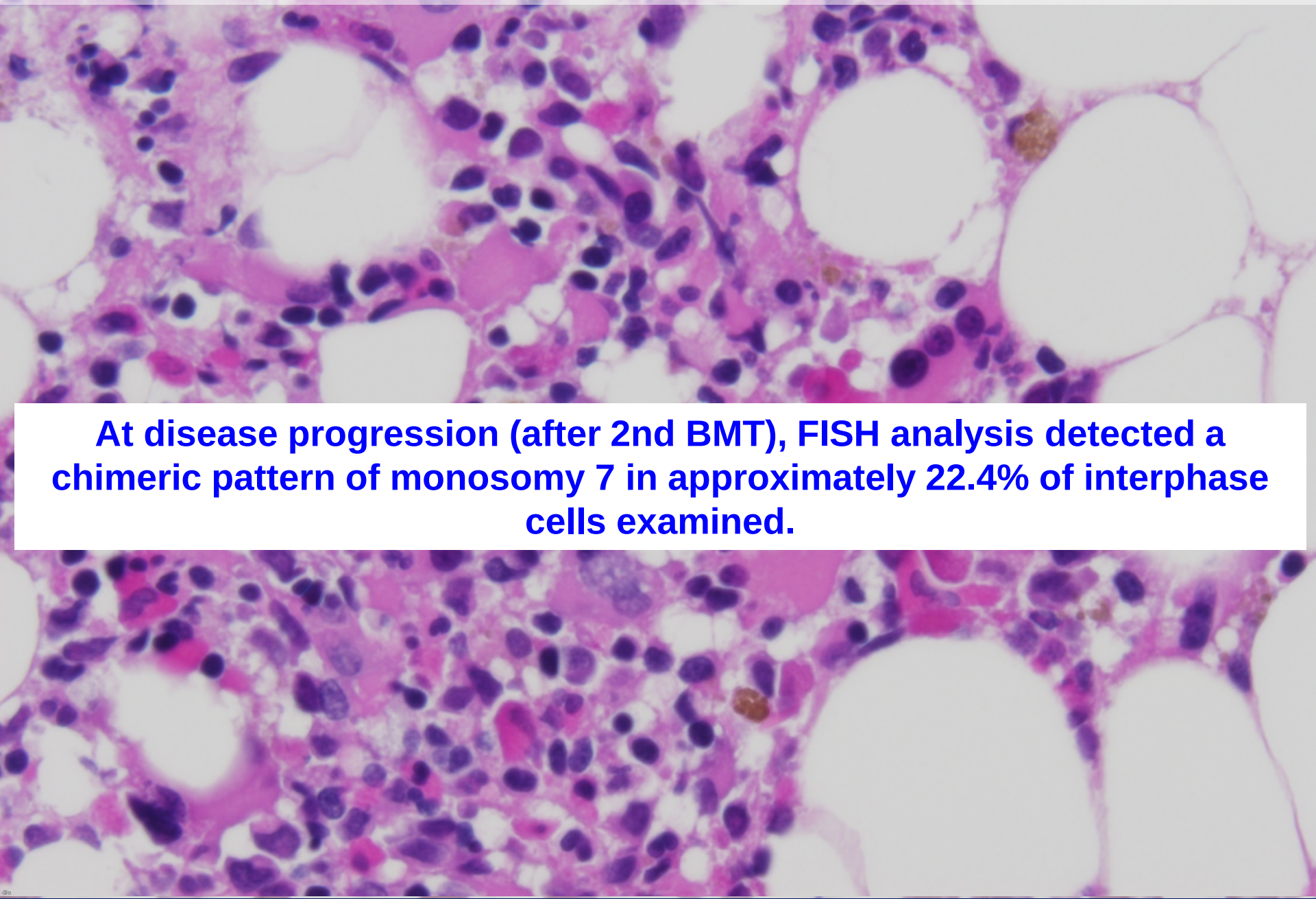


Fig. 2 *GATA2* germline mutations in children and adolescents with MDS. Structure of GATA2 protein with two functionally important zinc finger (ZF) domains marked in green (ZF1) and red (ZF2). 42 germline *GATA2* mutations are depicted, as previously reported by Wlodarski et al. [6]. *Red-color circles* represent affected amino acids. *Numbers* in *brackets* indicate the numbers of cases with a particular variant. *Bold font* denotes nonsense mutations, whereas *bold italic font* demonstrate splice site mutations

S. Hirabayashi et al. Int J Hematol (2017) 106: 175-182.

Fig 5: at disease progression (s/p 2nd BMT), bone marrow biopsy showed megakaryocytic hyperplasia and dysplasia.



At disease progression (after 2nd BMT), FISH analysis detected a chimeric pattern of monosomy 7 in approximately 22.4% of interphase cells examined.