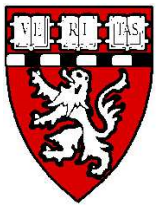
# *Inherited Predisposition to Myeloid (and Hematological) Malignancies*

**Mark D. Fleming, MD, DPhil**
*Department of Pathology*
*Boston Children's Hospital*
*Harvard Medical School*




## Inherited/Familial Predisposition to Hematological Malignancies (FPHM): How did we get here?

- Increasing understanding of the germline risk of cancer
- Exponential growth of utilization of next-generation sequencing panels/exomes/genomes in pathology
- Increased likelihood of encountering an "incidental" finding

# FPHM general principles

- **Syndromic or non-syndromic**
  - Absence of extra-hematopoietic features doesn't exclude a diagnosis
    - Some diagnoses are characteristically non-syndromic
  - Classically syndromic causes are sometimes clinically non-syndromic
- **Often autosomal dominant with incomplete penetrance/expressivity**
  - Occult familial disease, *e.g.,* parent with macrocytosis without anemia
  - Absence of a family history doesn't exclude the diagnosis
- **Often *de novo* dominant mutations**
  - Not strictly speaking "familial"
  - True of both syndromic and non-syndromic causes
- **Association with other hematological disorders**
  - Lymphoid malignancies (subset)
  - "Aplastic anemia" (? Hypocellular MDS misdiagnosis)
- **Wide age range**
  - "Congenital" diseases can present in late adulthood
  - Infants to older adults
  - Younger patients are more often syndromic
  - …But MDS/AML may be the presenting feature of a young adult with a "classic" bone marrow failure syndrome (*e.g.,* Shwachman-Diamond Syndrome)

# Keys to a timely diagnosis of FPHM

- **Familiarity with the diagnoses/syndromes**
  - *"Chance favors the prepared mind."*: Louis Pasteur
- **Familiarity with the genes**
  - Somatic mutations in some FPHM genes are common in sporadic hematological malignancies and are included on "somatic" next generation sequencing panels
  - Germline mutations are often discovered incidentally (*e.g., RUNX1, CEBP, GATA2*….)
  - Many germline mutations are reported as variants of unknown significance (VUS) on "somatic" sequencing panels
    - Analysis pipelines not specifically designed to evaluate germline variants
    - Evaluators are not necessarily aware of the syndromes or the patient's history
- **Having a high index of suspicion**
  - Infant/toddler with AMKL→ Down Syndrome or Trisomy 21 mosaicism
  - MDS/AML with monosomy 7 in a teenager → GATA2 deficiency
  - MDS with monosomy 7 in a toddler → SAMD9 or SAMD9L
  - JMML → Noonan Syndrome, NF1
  - tMDS → hereditary cancer predisposition syndrome, *e.g.,* Li-Fraumeni
- **Access to CLIA sequencing with well curated genes/variants**
- **Access to a multidisciplinary team**
  - Genetic counseling
  - Other subspecialists, including pulmonologists, endocrinologists, gastroenterologists

# Why test for FPHM?

- **Anticipate personal/familial risk**
  - Heme malignancies
  - Other cancers
  - Non-malignant complications (*e.g.,* pulmonary fibrosis)
- **Individual surveillance for disease progression**
  - Periodic CBCs/BMs well accepted
    - Certain cytogenetics associated with disease progression (*e.g.*, +3 in FANC)
  - Role of surveillance for mutations "characteristic" of disease progression uncertain
    - *e.g.*, TP53 mutations nearly universal in Shwachman-Diamond Syndrome AML
- **Determine appropriate therapy**
  - Avoid specific chemotherapies/XRT
  - Avoid inappropriate therapies
    - *e.g.*, immune suppression in aplastic anemia vs. hypoplastic MDS
- **HSCT donor selection**
  - Age-dependence and variable penetrance makes clinical assessment unreliable
- **Increasingly recognized as the standard of care for new diagnoses**
  - National Comprehensive Cancer Network (NCCN) MDS treatment guidelines
  - European LeukemiaNet AML treatment guideline
  - 2016 WHO Classification of Myeloid Malignancies

# 2016 WHO Classification of Myeloid Neoplasms with Germ Line Predisposition

- **Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction**
  - AML with germ line *CEBPA* mutation
  - Myeloid neoplasms with germ line *DDX41* mutation*
- **Myeloid neoplasms with germ line predisposition and preexisting platelet disorders**
  - Myeloid neoplasms with germ line *RUNX1* mutation*
  - Myeloid neoplasms with germ line *ANKRD26* mutation*
  - Myeloid neoplasms with germ line *ETV6* mutation*
- **Myeloid neoplasms with germ line predisposition and other organ dysfunction**
  - Myeloid neoplasms with germ line *GATA2* mutation
  - Myeloid neoplasms associated with BM failure syndromes
  - Myeloid neoplasms associated with telomere biology disorders
  - JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
  - Myeloid neoplasms associated with Down syndrome*

**Lymphoid neoplasms also reported*

Adapted from Table 17, Arber *et al.* Blood 2016 127:2391-2405

# FPHM: Phenotypic Rubric

- **FPHM without other organ dysfunction *(i.e., non-syndromic)***
  *CEBPA* *DDX41* *RBBP6*
- **FPHM with other organ dysfunction (*i.e., syndromic*)**
  *ATG2P-SKP2* *ATM* *BLM* *BRCA1* *BRCA2* FANC genes
  *GATA2* *TP53* *SAMD9* *SAMD9L*
- **FPHM associated with platelet dysfunction/thrombocytopenia**
  *RUNX1* *ANKRD26* *ETV6*
- **FPHM due to telomere biology disorders (*i.e.,* Dyskeratosis Congenita)**
  *DKC1* *TERC* *TERT* *CTC1* *RTEL1* *Others*
- **Diamond-Blackfan Anemia**
  *RPLs* *RPSs* *ADA2*
- **Congenital Neutropenia**
  *SBDS* *ELANE* *HAX1* *? Others*
- **Noonan syndrome**
  *PTPN11* *CBL* *KRAS* *NRAS* *Others*
- **Neurofibromatosis 1**
- **Trisomy 21**

Adapted from Table 1 Brown *et al.* Seminars in Hematology 54 (2017) 60–6)

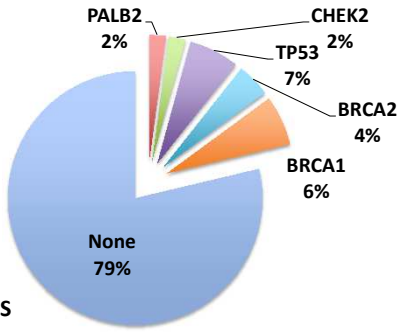
# Pathways involved in FPHM

- **Transcription Factors**
  CEBPA ETV6 GATA2 RUNX1
- **DNA Repair Enzymes/Factors**
  ATM BRCA1 BRCA2 FANCA FANCB FANCC…
- **Helicases**
  BLM DDX41
- **RAS Signaling**
  NF1 PTPN11 CBL KRAS NRAS Others
- **Ribosome Biology**
  SBDS RPSs RPLs
- **Telomere Biology**
  DKC1 TERC TERT CTC1 RTEL1 Others
- **Other or Multiple Pathways**
  ATG2P-GSKIP RBBP6 ELANE ANKRD26
  SAMD9 SAMD9L Trisomy 21

Adapted from Table 2, Brown *et al.* Seminars in Hematology 54 (2017) 60–68)

# Personal/Family History in FPHM

- **Personal history of multiple cancers**
  - Patients with tAML/MDS
  - "Solid tumor" syndromes predispose to tMN
- **Familial "solid tumor" syndromes are associated with MDS/AML/tMDS**
  - *BRCA1/BRCA2*: breast, ovary, prostate cancers
  - *TP53*/Li-Fraumeni: Sarcomas (especially osteosarcoma), adrenal cortical carcinoma, pre-menopausal breast cancer
  - Telomere disorders: Mucosal squamous cancers




**Germline Familial Breast Cancer Mutations in tMDS**

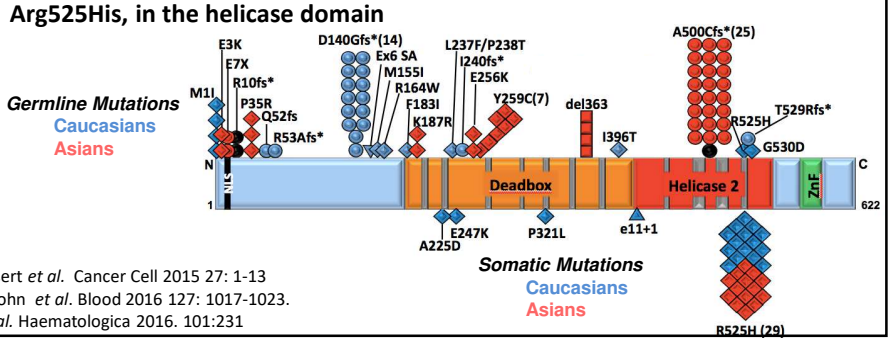
Figure adapted from Churpek *et al. Cancer* 122: 304-311, 2016

# Personal/Family History in FPHM (cont)

- **History of thrombocytopenia/platelet dysfunction**
  - Especially with a family history of MDS/AML/ITP
  - Bleeding is often "out of proportion" to the platelet count
  - Be skeptical of a prior diagnosis of ITP in a patient with MDS/AML
- **Early onset of malignancies typical of older individuals**
  - Median age of MDS = 71 yo
  - Monosomy 7, especially in an individual <30 yo with no prior history
- ***Anything* syndromic and uncommon should be suspicious**
  - Neurological abnormalities: Ataxia-Pancytopenia
  - Endocrinopathies: MIRAGE, Fanconi Anemia
  - Growth failure: Fanconi Anemia, Shwachman-Diamond Syndrome
  - Pulmonary fibrosis: telomeropathies
  - Skeletal abnormalities: Shwachman-Diamond Syndrome, Fanconi Anemia, MECOM
  - Urogenital abnormalities: Diamond-Blackfan Anemia, Fanconi Anemia, MIRAGE
  - Peculiar or persistent infections: chronic warts, atypical mycobacterial infection → *GATA2*
- **Evidence of genetic anticipation**
  - Earlier presentations and more severe phenotypes (especially telomeropathies)

# Familial AML due to *DDX41* mutations

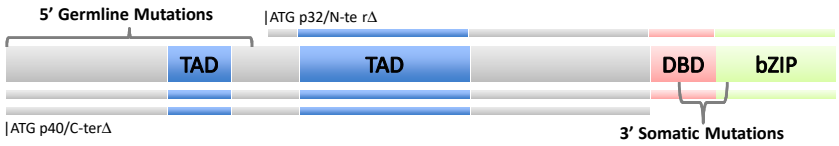
- **DDX41 is an RNA helicase involved in altering RNA secondary structure in a wide variety of cellular processes including mRNA splicing**
- **Average age of AML/MDS diagnosis: 62yo**
  - Also associated with pediatric ALL
  - Some mutations may also predispose to other lymphoid malignancies and/or colon/gastric cancer
- **Germline allele often a null allele**
  - Distinct, recurrent (? Founder) alleles present in Caucasians and Asians
- **Somatic mutation nearly always a particular missense variant, Arg525His, in the helicase domain**




Polprasert *et al.* Cancer Cell 2015 27: 1-13
Lewinsohn *et al*. Blood 2016 127: 1017-1023.
Li R *et al.* Haematologica 2016. 101:231

# Familial AML due to *CEBPA* mutations

- **CCAAT binding enhancer bZIP transcription factor**
- **Non-syndromic, nearly completely penetrant phenotype (AML)**
  - Age of onset of AML ~2-50 yrs.
- **Normal karyotype AML with a good prognosis: 70% 5-year OS**
- **Germline allele is typically a 5' truncation**
  - Uses an internal ATG an a protein (p32) without one of its two transactivation domains (TAD).
  - C-terminal germline mutations do occur, but are thought to be less penetrant
- **AML typically has a "second hit" 3' somatic mutation resulting in a protein without the dimerization and DNA binding (DBD) domains**
  - *GATA2* and *WT1* are often (mutually exclusively) seen as additional somatic events
- **Germline mutations are present in ~11% of patients presenting with biallelic CEBPA mutations**
  - *i.e.*, rule out a germline mutation in a patient with a biallelic *CEBPA* mutations!
- **Relapses are often a *second* leukemic event with a distinct clonal somatic mutation**
  - Argument can be made that HSCT should be performed in first remission due to risk of second AML




Pabst *et al.* JCO 2008. 26:5088-93, Tawana *et al.* Blood 2015. 126:1214-23, Taskesen *et al.* Blood 2011. 117:2469-75, Figure adapted from Tawana *et al.* Semin Hematol. 2017. 54:87-93

# Familial Platelet Disorders (FDPs) with Predisposition to Hematological Malignancies

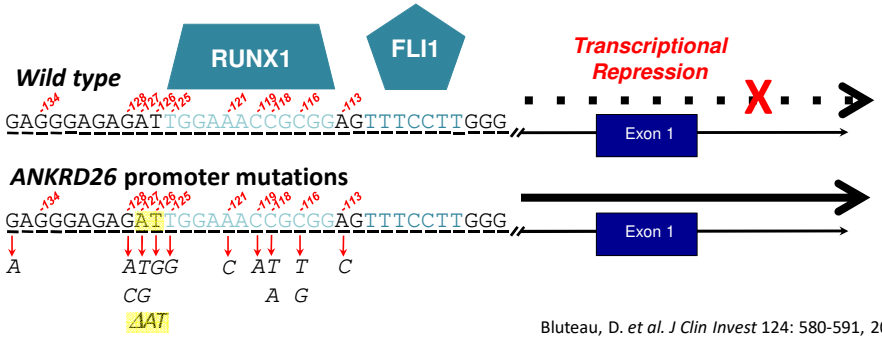
- **Autosomal dominant disorders with variable penetrance**
  - *RUNX1*, *ANKRD26*, and *ETV6* mutations
- **Generally <u>not</u> syndromic**
  - *i.e., unlike* several other dominant familial thrombocytopenia, *e.g.*, *MYH6* disorders, 11q23 deletions, etc…
  - Macrodeletions of the *RUNX1* gene and contiguous genes leads to a complex developmental disorder apparent in infancy
- **Often mistaken for ITP**
  - Platelet size is typically normal (not large)
  - Platelet count often not critically low, but patients experience bleeding episodes
  - Often have demonstrable platelet function defects
    - PLT count may never be high enough to test, therefore missed.
- **Associated with increased susceptibility to myeloid and lymphoid malignancies**
  - Some families have few cases of malignancies: thrombocytopenia only
  - *ETV6* mutations may also be associated with GI malignancies

# FDP associated with *RUNX1* mutations

- **Mild to moderate thrombocytopenia**
- **"Aspirin-like" platelet aggregation defect with abnormal δ-granules**
- **Missense, nonsense, splicing, deletion mutations throughout the gene**
- **35-40% estimated lifetime risk of a hematological malignancy with median age of onset of 33 yrs. (6-75 yrs.)**
  - MDS/AML>>lymphoid
  - T-ALL not uncommon
- **Dysplastic megakaryocytes not uncommon at "baseline," but it is unclear if this is related to the evolution of clonal hematopoiesis.**
  - Incidence of clonal hematopoiesis 80% @ age 50 yrs.
  - Often associate with secondary mutations in chromatin remodeling genes (*e.g.*, *DNMT3A*)
- **Diverse somatic mutations in germline *RUNX1*-associated AML**
  - Second hit in *RUNX1*
    - Copy neutral LOH
    - Duplication of the mutated allele
    - Somatic mutation of RUNX1 on the other copy
    - Consider the possibility of one germline allele in the patient with "sporadic" AML and two *RUNX1* mutant alleles.
  - Epigenetic modifiers and other transcription factors
    - *ASXL1, BCOR, DNMT3A, PHF6*
    - *WT1, GATA2, FLI1*

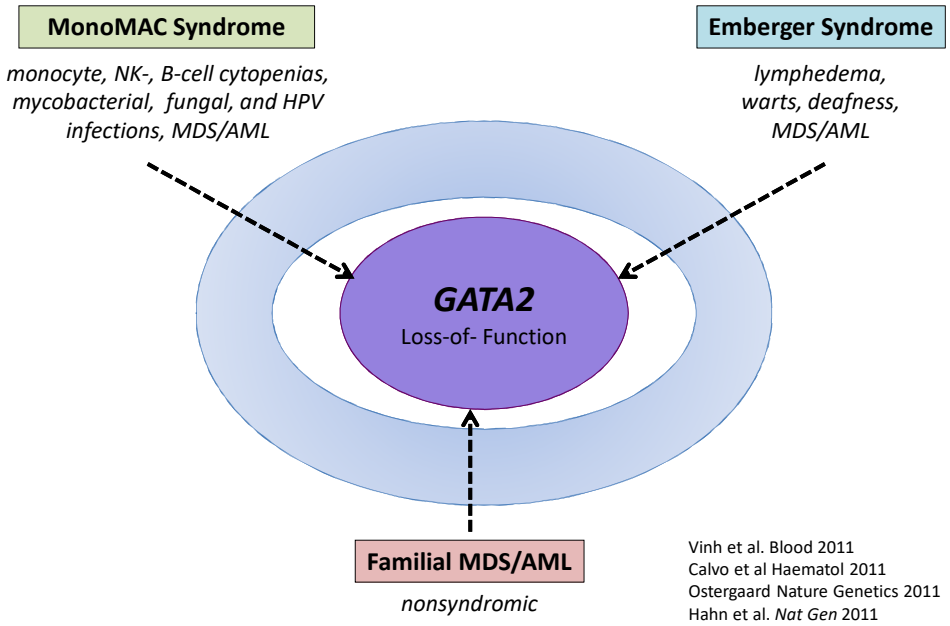
# *ANKRD26* promoter mutations

- Ankyrin repeat domain 26: function not entirely clear
- Moderate thrombocytopenia
- Variable platelet aggregation defects including to arachidonate, ADP, and $Ca^{+2}$ ionophores. Decrease in α-granules
- MDS/AML>>CML, CLL, CMML
- Increased and dysplastic megakaryocytes
- Point mutations in the promoter disrupt RUNX1- and FLI1-dependent transcriptional repression.




Bluteau, D. *et al. J Clin Invest* 124: 580-591, 2014

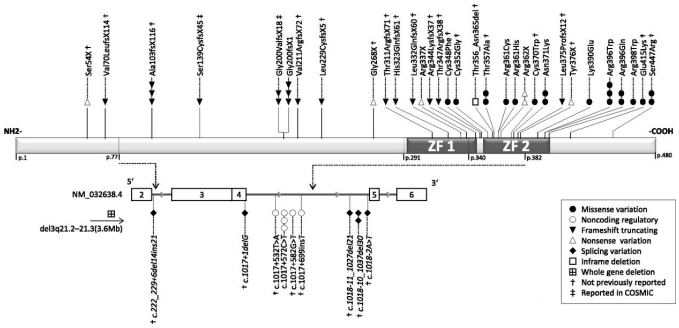
# *GATA2* mutation associated diseases



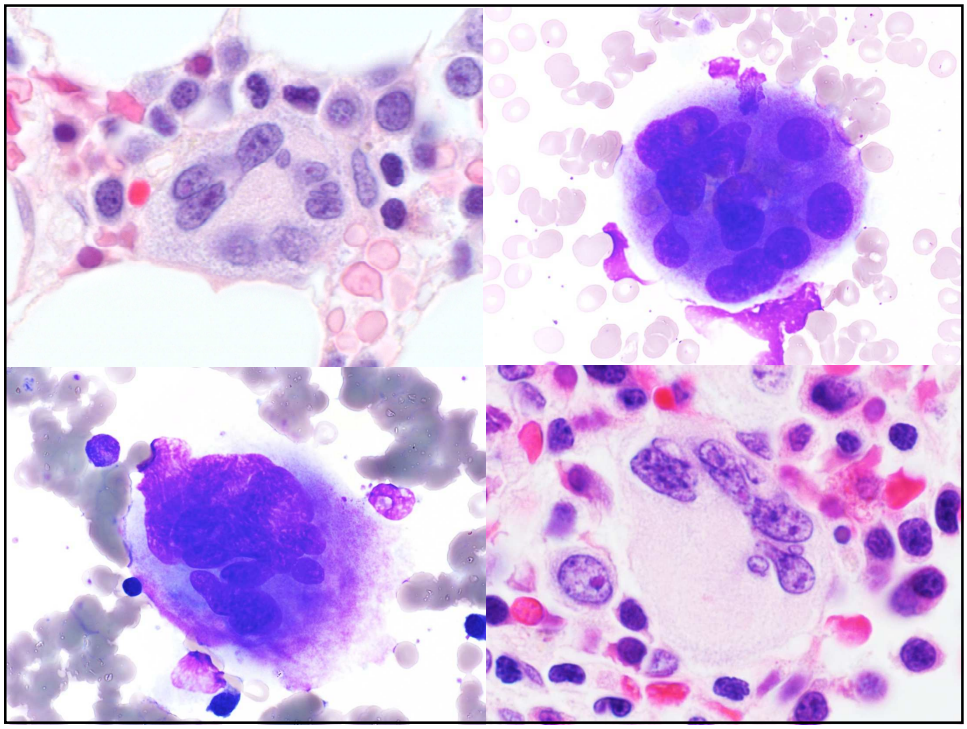

Vinh et al. Blood 2011
Calvo et al Haematol 2011
Ostergaard Nature Genetics 2011
Hahn et al. *Nat Gen* 2011

# Germline *GATA2* Mutations in MDS/AML

- **GATA2 is a transcription factor important in hematopoietic and vascular development that regulates specification of the myeloid vs. erythroid lineage**
- **Loss of function/haploinsufficiency phenotypes**
  - No definite genotype-phenotype correlation
- **Point mutations cluster in the zinc fingers (ZF) important for DNA binding**
- **Deletions and intron 4 enhancer mutations are common**
  - Not detected by exome sequencing

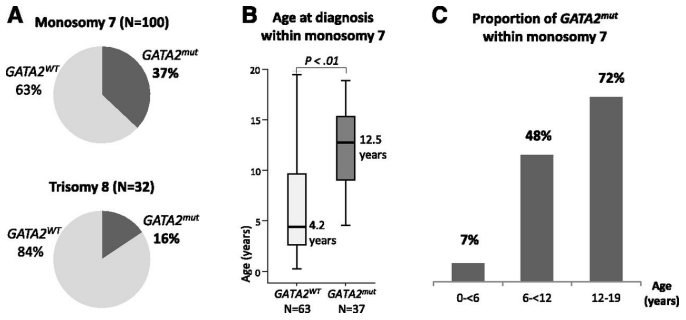



Wlodarski et al. Blood 2016;127:1387-1397, Figure 3A, used with permission of the author



# *GATA2* MDS/AML

- **Commonly seen in MDS in children: 28/426 cases of primary MDS**
  - Hypocellular MDS (*i.e.*, refractory cytopenia of childhood/RCC) may be diagnosed as aplastic anemia
- **Transformation to MDS/AML associated with monosomy 7 and trisomy 8**
  - Germline *GATA2* mutations highly associated with monosomy 7 in teenagers
  - ASXL1 somatic mutations associated with high-grade MDS
- ***GATA2* mutation has no impact on outcome in patients treated with HSCT**
  - Diagnosis impacts selection of HSCT donor



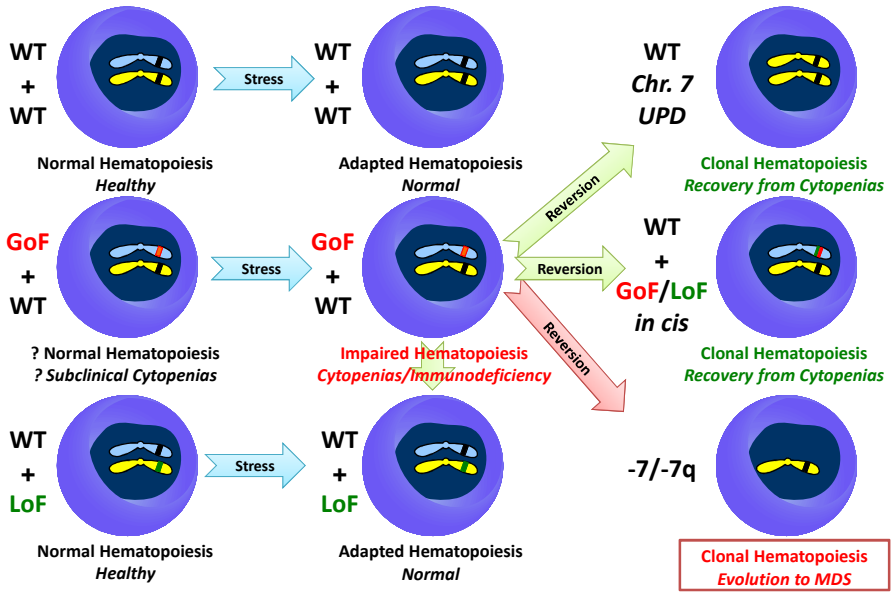

Wlodarski *et al.* Blood 2016;127:1387-1397, Figure 2, used with permission of the author

# *SAMD9/SAMD9L*

- ***Sterile Alpha Motif Domain 9* and *9-Like***
  - Located in tandem on chromosome 7q21
- **SAMD9: MIRAGE Syndrome**
  - **M**yelodysplasia
  - **I**nfection
  - **R**estriction of growth/IUGR
  - **A**drenal hypoplasia
  - **G**enital phenotypes
  - **E**nteropathy
  - *Usually de novo* dominant mutations: sometimes dominant with reduced penetrance
- **SAMD9L: Ataxia-Pancytopenia Syndrome**
  - Cerebellar ataxia
  - Pancytopenia/MDS
  - Sometimes no neurological findings
  - Often clearly familial with dominant inheritance
- **SAMD9/SAMD9L gain of function (GoF) alleles**
- **Major contributors to MDS with monosomy 7 in early childhood**
- **Reversion mutations may lead to milder phenotypes or MDS with monosomy 7**

Narumi *et al. Nature Genet 2016* 48: 792-797, 2016, Chen. *et al. Am J Hum Genet 2016* 98:1146-1158

## Clonal Evolution in *SAMD9/SAMD9L*




Modified from Tesi *et al.* Blood 2017. 129: 2266-2279

## Final Messages

- **Consider the possibility of a germline predisposition to hematological malignancy in all patients. It's more common than you might think**


- *Acknowledgements to Lucy Godley, MD for providing material for this presentation*


THANK YOU!


mark.fleming@childrens.harvard.edu