Myeloid proliferation associated with Down syndrome

*Transient myeloproliferative disorder (TMD):* Affects approximately 10% of infants with Down syndrome.

- Increase of megakaryocytic blasts in blood in newborn babies.
- Symptoms include thrombocytopenia, leukocytosis (with blasts), hepatosplenomegaly.
- Spontaneous remission within first 3 months

*Acute myeloid leukemia:* Affects 1-2% children with Down syndrome, 20-30% children with TMD develop acute myeloid leukemia

- Vast majority are <5 years of age
- Symptoms include thrombocytopenia, leukocytosis (with blasts), hepatosplenomegaly.
- May present as MDS or AML, but there are no biologic differences
- Megakaryocytic differentiation >50% cases

**Morphology**

- Blasts: Large blasts with basophilic cytoplasm, cytoplasmic blebbing, variable number of coarse basophilic granules
- Erythroid dysplasia common
- Bone marrow with prominent reticulin fibrosis, megakaryocytic dysplasia

**Phenotype:** Megakaryoblastic phenotype: CD41+, CD42+, CD61+, CD13+, CD33+, CD34+, CD117+, HLA-DR+, MPO-

**Genetics:** Trisomy 21. Subset GATA1 mutated.

**Prognosis:** TMD: Self limited
- AML: Young children have good prognosis. Older children have comparable prognosis to those without Down syndrome
  (Additional discussion in lesson 23)

**Myeloid neoplasms associated with Fanconi anemia**

Acute myeloid leukemia and myelodysplastic syndrome arising from Fanconi anemia patients 600-800 folds of increased risk as compared to normal children

- Most patients have one or several characteristic physical features: short stature, radial abnormality, microphthalmia, ear abnormality, deafness, café-au-lait spots, and anemia/pancytopenia (bone marrow failure)

**Morphology:** Typical myeloblasts morphology, multilineage dysplasia

**Phenotype:** CD13+, CD33+, CD34+, CD117+, HLA-DR+

**Genetics:** Mutations of one of the *FANC* genes. Chromosome breakage analysis (screen)

**Prognosis:** Unfavorable

**Other related disorders:** Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, dyskeratosis congenita

**Myeloid neoplasms associated with Germline Gata2 mutation**

Inherited or congenital disorders with protean manifestations

- Median age of presentation 20 years old
- Clinical presentation includes infection, aplastic anemia, MDS/AML, lymphaedema

**Associated syndromes:**
**MonoMac syndrome**: Monocytopenia, non-TB mycobacterial infection

**DCML deficiency syndrome**: Deficiency of dendritic cells, monocytes, B and NK cells, prone to viral infections

**Familiar MDS/AML**: Myelodysplastic syndrome, acute myeloid leukemia

**Emberger syndrome**: Primary lymphedema, warts, predisposition to MDS/AML

**Morphology**: Typical myeloblasts morphology, multilineage dysplasia

**Phenotype**: CD13+, CD33+, CD34+, CD117+, HLA-DR+

**Genetics**: GATA2 mutations present in coding or non-coding regions. Full gene sequencing necessary for diagnosis

**Prognosis**: Unfavorable

---

### Myeloid neoplasms associated with inherited disorders

**Myeloid neoplasms with germline predisposition with thrombocytopenia**

AML and MDS with germline mutations of *RUNX1, ANKRD26, or ETV6*

Autosomal dominant inheritance

Prevalence unknown

Associated with various degrees of thrombocytopenia and abnormal platelet function in childhood:

*RUNX1* mutated cases: associated with abnormal platelet aggregation with collagen and epinephrine, dense granule storage pool deficiency

*ANKRD26* mutated cases: associated with glycoprotein Ia deficiency, alpha granule deficiency

*ETV6* mutated cases: no specific association

May also increase susceptibility of lymphoid neoplasm and solid tumors

**Morphology**: Typical myeloblasts morphology, multilineage dysplasia

**Phenotype**: CD13+, CD33+, CD34+, CD117+, HLA-DR+

**Genetics**: germline mutation of *RUNX1, ANKRD26, ETV6*

Second *RUNX1* or other gene mutation common (second hit)

**Prognosis**: Unknown

**Genetic Counselling**: Increased bleeding tendency in patient and affected family members

Clinical significance includes donor selection (related donors) for hematopoietic stem cell transplant

---

**Myeloid neoplasms with germline predisposition without pre-existing disorder**

AML and MDS with germline mutations of *CEBPA* or *DDX41*

Autosomal dominant inheritance

Prevalence unknown

Typical cases are biallelic mutated, with one germline mutation and second somatic mutation

*CEBPA*: Affects children or young adults, mean age of disease 25 y/o

*DDX41*: Long latency, mean age of disease 62 y/o, predominantly high grade diseases (high grade MDS, AML, MDS with 5q-)

May also increase susceptibility to lymphoid neoplasms and solid tumors

**Morphology**: *CEBPA*: Typical myeloblast morphology

*DDX41*: Low WBC, hypocellular bone marrow, prominent erythroid dysplasia

**Phenotype**: CD13+, CD33+, CD34+, CD117+, HLA-DR+

**Genetics**: *CEBPA*: Germline mutation at 5’ end, somatic mutation at 3’ end, normal karyotype

*DDX41*: Germline mutation at 5’ end and DEAD box, somatic mutation at helicase domain (3’ end). *DDX41* is located at chromosome 5q and deleted 5q may serve as 2nd hit

**Prognosis**: *CEBPA* favorable. *DDX41* poor
Genetic Counselling: Clinical significance includes donor selection (related donors) for hematopoietic stem cell transplant