Fanconi Anemia
Symptoms, Genetics, Diagnosis and Treatment

Symptoms - Congenital Abnormalities - Very heterogeneous
- Hand and arm abnormalities (71%)
- Skeletal anomalies (hips, spine) (71%)
- Skin discolouration (64%) (hips, spine) (71%)
- Short stature (63%)
- Mental retardation (16%)
- Gastrointestinal difficulties (14%)
- Hearing (11%)
- No abnormalities (30%)

Haematopoetic Abnormalities (next lecture)
- Bone marrow failure
- Aplastic anemia
- Susceptibility to infections

Predisposition to cancer
- Leukemia early on
- Cancers of rapidly dividing tissues (mouth, esophagus, GI tract, anus)

Fanconi Anemia - Timeline
Often apparent at birth due to congenital abnormalities.
If not, disease usually manifests by age of 12. Rare cases, no symptoms before adulthood.
73% have overt bone marrow disease by age 10, mean age 7 or 8.
Median survival is 7 yrs after development of overt bone marrow disease.

Molly Nash
Molly Nash was diagnosed shortly after birth. She was born with hand abnormalities, hip dislocation, deafness in the left ear, heart and intestinal abnormalities.
Pancytopenia was observed at age 2.
Bone marrow failure developed at age 3.
Myelodysplasia (pre-leukemia) developed at age 4.

Genetics
Fanconi Anemia is an autosomal recessive disease.
Mutations in 11 different genes can lead to Fanconi Anemia.
All genes are in a DNA repair pathway.
Molecular mechanism by which these mutations lead to FA are not clear.

Most commonly mutated genes
- FANCA (66%)
- 100 different mutations
- FANCC (12%)
- IVS 4+4 A T
  common in Ashkenazi Jews
- 1 in 89 carries
  common in Japanese
  FANCG (12%)

Today we will address a case involving the IVS4+4 mutation.
The FANCC gene is on chromosome 9.
The FANCC gene delays the onset of apoptosis.
Promotes homologous recombination repair of damaged DNA.
The FANCC gene has 1,674 bp of coding sequence.
14 exons, 53 to 204 bp in length.

In the 4th intron, an A is replaced by a T leading to an altered splice site and deletion of exon 4 in the FANCC protein.

Diagnosis
FA is diagnosed by a chromosome breakage test.
Lymphocytes are cultured in the presence of mitomycin C and observed for excess chromosome breakage.
**Treatment**

Bone Marrow Transplant (BMT): Cells from the patient's bone marrow are replaced by someone else's cells. Cells from a donor's bone marrow or umbilical cord blood can serve as a source for the transplant. The 2 year survival rate following BMT in FA patients is variable:
- 60 - 85% with a matched sibling donor
- 20 - 40% with a donor from a bank.

**Molly Nash**

Umbilical cord blood from her matched brother served as the source for donor cells. With a bone marrow transplant, Molly Nash is doing well. She attends school, dances, plays soccer. She no longer has anemia, and is no longer at risk for leukemia (her new bone marrow cells do not have the mutation). However, she still needs treatment for intestinal and spinal abnormalities and she is at risk for various cancers later in life.