

Fanconi Anemia

Background Info

Symptoms, Genetics, Diagnosis and Treatment

Symptoms - Congenital Abnormalities - Very heterogeneous

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



Haematopoietic Abnormalities (next lecture)

- Bone marrow failure
 - aplastic anaemia
 - 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

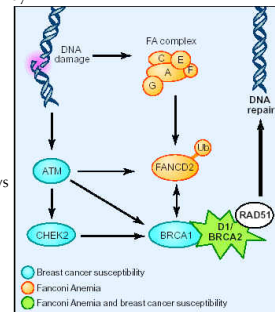


Genetics

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

Both of the parents have the same FANCC mutation, ivs4+4.

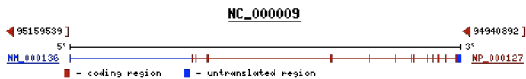
The FANCC gene is on chromosome 9

FANCC

- delays the onset of apoptosis
- promotes homologous recombination repair of damaged DNA

FANCC gene has 1,674 bp of coding sequence

14 exons, 53 to 204 bp in length

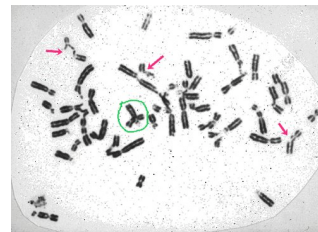


in the 4th intron, an A is replaced by a T leading to an altered splice site and deletion of exon 4 in the FANCC protein.

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.