

# Inherited Bone Marrow Failure Syndromes

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## **Diamond-Blackfan Anemia (DBA)**

DBA patients have only low red cell counts (anemia). The rest of their blood cells (the platelets and the white cells) are normal.

25% of DBA patients have physical abnormalities, often involving malformations of the thumbs. Most patients are diagnosed within the first year of life. Detecting a mutation in a known DBA gene confirms the diagnosis.

However, failure to find a mutation in a DBA gene does not eliminate the diagnosis of DBA. This is because the genes which have been identified so far explain less than half of the disease occurrences. Currently, DBA is diagnosed by clinical findings after exclusion of other known causes of pure red cell anemia. Males and females are affected equally.

1. What are the major findings on physical examination?
  - a. Short stature
  - b. Abnormal thumbs
2. What is the age at diagnosis?
  - a. Anytime from birth to 60 years of age.
  - b. 90% are less than 1 year old when the diagnosis is made.
3. What is the pattern of bone marrow failure?
  - a. Pure anemia (low red blood cell count, often with large red cells)
  - b. Normal platelet count usually (Platelets are the cells in the blood which help the blood to clot)
  - c. Normal white cells usually (White cells help the body fight off infection)
4. What specific kinds of cancer develop?

- a. Leukemia (cancer of the blood and bone marrow)
  - b. Sarcomas (cancer arising in bone, fat, cartilage, tendons or connective tissue)
5. How DBA is specifically diagnosed?
- a. Patients with DBA usually have an increase in a specific red cell enzyme called adenosine deaminase (ADA).
  - b. Mutation analysis (genetic testing)
    - i. Laboratories can now identify the genetic “error” (or mutation) in some patients.
    - ii. There are more than 3 different genes responsible for DBA: *RPS19*, *RPS24*, *RPS17* and others.
    - iii. The disease is inherited in an autosomal dominant fashion. This means that illness may occur if a person has only one copy of the abnormal (mutant) gene.

## **Dyskeratosis Congenita (DC)**

DC patients have characteristic abnormal shapes to fingernails and toenails, a lacy rash on the face and chest, and white patches in the mouth. 75% of the patients are males. About half of DC patients develop bone marrow failure. Onset may be in early childhood, but diagnoses are often made later, because the findings on physical examination become more obvious with age. Several genes have now been identified as causing DC, but there are more still to be discovered.

1. What are the major findings on physical examination?
  - a. Abnormal fingernails and toenails (dyskeratosis)
  - b. Lacy rash on the face, neck, and chest
  - c. White patches in the mouth (leukoplakia)
2. What is the age at diagnosis?
  - a. From birth to 60 years of age or older
  - b. The diagnosis is usually made between the ages of 10 to 30 years.
3. What is the pattern of bone marrow failure?

- a. Aplastic anemia is diagnosed when all 3 types of cells (red cells, white cells and platelets) are abnormally low because the bone marrow is not producing them.
  - b. Anemia (low red blood cell count) may develop (often with large red cells).
  - c. Low platelet count (platelets are the cells which help the blood to clot)
  - d. Low white cell count (white cells help the body fight off infection)
4. What specific kinds of cancer develop?
- a. Solid organ cancer
    - i. Tongue, mouth and throat cancer (“head and neck”)
    - ii. Cancer of the esophagus, stomach, colon, and rectum (“gastrointestinal”)
    - iii. Perhaps others (all of the types of solid cancers associated with DC have not been completely identified)
  - b. Leukemia (cancer of the blood and bone marrow)
5. How DC is specifically diagnosed?
- a. Characteristic findings on physical examination
  - b. Telomere length testing (repeated sections of DNA at the ends of chromosomes are short in patients with DC).
  - c. Mutation analysis (genetic testing)
    - i. Laboratories can now identify the genetic “error” (mutation) in some patients.
    - ii. The type of DC that is inherited only by males (X-linked inheritance) is usually due to mutations in the gene called *DKC1*.
    - iii. The type of DC that is passed from an affected parent to an affected child (autosomal dominant inheritance) may be due to mutations in other genes called *TERC*, *TERT* and *TINF2*.
    - iv. One gene has been identified for the type of DC in which disease occurs only if a person has **two**

abnormal genes (autosomal recessive inheritance), called *NOP10* (also known as *NOLA3*).

- v. Some patients have no mutations in the known genes; more genes await discovery.

6. What are DC subsets?

- a. Hoyeraal-Hreidarsson (HH) Syndrome: Findings consistent with DC, plus intrauterine growth retardation, developmental delay, microcephaly (small head), cerebellar hypoplasia, immunodeficiency, and bone marrow failure. Some HH patients have mutations in *DKC1* or *TERT*.
- b. Revesz Syndrome: Findings similar to HH, plus a specific finding in the eye, called “exudative retinopathy”. One patient had a mutation in *TINF2*.

## Fanconi Anemia (FA)

FA patients have relatively specific physical findings in 75% of affected persons. Laboratory findings include aplastic anemia, increased chromosome breakage in cells grown in the presence of a chemical which damages DNA, mutation in one of the 13 separate genes which have been identified (“cloned”), or assignment to one of the sub-categories into which patients with FA can be classified (known as “complementation groups”). Bone marrow failure is NOT required for the diagnosis, and 25% of all persons eventually diagnosed as being affected by FA do not have the typical FA findings on physical examination. FA has been diagnosed at ages ranging from birth to >50 years of age. Males and females are affected equally.

- 1. What are the major findings on physical examination?
  - a. Cafe au lait spots (brown birth marks)
  - b. Short stature
  - c. Abnormal thumbs, often including abnormal radii (these are the bones in the lower arm, between the elbow and the wrist)

- d. Abnormal male development, infertility
  - e. Small head
  - f. Small eyes
  - g. Abnormal kidneys
2. What is the age at diagnosis?
- a. Anytime from birth to 50 years of age
  - b. Usually by age 10 to 15 years
3. What is the pattern of bone marrow failure?
- a. Often called aplastic anemia, which is diagnosed when all 3 types of cells (red cells, white cells and platelets) are abnormally low because the bone marrow is not producing them.
  - b. Low red cell count (“anemia”, often with large red cells)
  - c. Low platelet count (platelets are the cells in the blood which help the blood to clot)
  - d. Low white cell count (white cells help the body fight off infection)
4. What specific kinds of cancer develop?
- a. Leukemia (cancer of the blood and bone marrow)
  - b. Liver tumors
  - c. Solid organ cancer
    - i. Cancers of the mouth, tongue and throat (“head and neck”)
    - ii. Cancers of the female genitals, particularly labial and cervical cancer (“gynecologic”)
    - iii. Cancer of the esophagus (“gastrointestinal”)
    - iv. Brain tumors
    - v. Possibly others
5. How FA is specifically diagnosed?
- a. The chromosome breakage test
    - i. The patient’s blood cells are treated in the laboratory with a chemical which damages (breaks) DNA (the basic chemical for all genes).
    - ii. The breaks are large enough to be seen under a microscope, and are counted.
  - b. Mutation analysis (genetic testing)

- i. Laboratories can now identify the specific genetic “error” (or mutation) in some patients, in genes called FANCX, where **X** stands for the FA complementation group A through N.
- ii. There are at least 13 different gene pairs (complementation groups) responsible for FA: *FANCA*, *FANCB*, *FANCC*, *FANCD1 (BRCA2)*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCI*, *FANCL*, *FANCM*, *FANCN*.
- iii. The disease is primarily inherited in an autosomal recessive manner (*FANCB* is X-linked, requiring inheritance of a mutant gene from the mother only). This means that illness occurs only if a person has two abnormal (mutant) genes from the same complementation group. One abnormal gene is inherited from each parent. Persons like the parents, who have only one copy of the abnormal gene, are called “gene carriers.”

### **Shwachman-Diamond Syndrome (SDS)**

SDS patients have poor food absorption (malabsorption) and low white blood cell counts (neutropenia). Most patients are diagnosed in infancy. Males and females are affected equally.

1. What are the major findings on physical examination?
  - a. Short stature
  - b. Problems with bones (“metaphyseal dysostosis”, a specific finding seen on x-rays).
2. What is the age at diagnosis?
  - a. The diagnosis of SDS is usually made in the first year of life.
3. What is the pattern of bone marrow failure?
  - a. Neutropenia (low white blood count; white cells help the body fight off infection)

- b. Anemia (low red blood cell count) may develop (often with large red cells).
  - c. Low platelet count may develop (platelets are the cells in the blood which help the blood to clot).
  - d. Aplastic anemia is diagnosed when all 3 types of cells (red cells, white cells and platelets) are abnormally low because the bone marrow is not producing them.
4. What specific kinds of cancer develop?
- a. Leukemia (cancer of the blood and bone marrow)
5. How SDS is specifically diagnosed?
- a. Reduced digestive enzyme production by the pancreas (“Pancreatic insufficiency”), which can be measured by various laboratory or x-ray tests:
    - i. Low serum trypsinogen and isoamylase (key digestive enzymes made by the pancreas)
    - ii. Abnormal amounts of fat in the stool
    - iii. Low pancreatic enzymes after stimulation of the pancreas
    - iv. Small or fatty pancreas on ultrasound or CT scan imaging of the pancreas
  - b. Bone marrow failure
    - i. Low neutrophils in blood on at least 3 occasions
    - ii. May have low hemoglobin and/or platelets
  - c. Genetic testing
    - i. The disease appears to be inherited in an autosomal recessive manner. This means that illness occurs only if a person has two abnormal (mutant) copies of the SDS gene. Laboratories can now identify the specific genetic “error” (or mutation) in some patients, in a gene called *SBDS*, which stands for Shwachman Bodian Diamond Syndrome.

## **Other Bone Marrow Failure Syndromes**

There are several other inherited bone marrow syndromes which are less common than the ones that are discussed individually on this Website. These diagnoses are usually made by experts in hematology or genetics. Examples include the following disorders: IVIC (named with the initials of the institution which first reported it), WT (after the initials of the first two families reported), radio-ulnar synostosis (the bones of the lower arm are joined together at the elbow), ataxia pancytopenia (unsteady walking and aplastic anemia). There are families with more than one case with bone marrow failure, who do not fit any of the usual categories. Finally, there are other genetic diseases in which bone marrow failure has been reported on rare occasions, but in which bone marrow failure is not thought to be a major feature of the disease. These include disorders such as Seckel syndrome, Dubowitz syndrome, and Down syndrome.

### **Pearson Syndrome**

Patients with Pearson Syndrome may have poor food absorption (malabsorption) and low white blood cell counts (neutropenia). Low red cell counts (anemia) can be a major problem, and low platelet counts (thrombocytopenia) can also occur. Symptoms are often present in infancy. Liver and kidney disease usually develop. Examination of the bone marrow under the microscope reveals characteristic holes (“vacuoles”) in many cells. The disease is caused by a loss, or deletion, of large pieces of DNA from tiny structures in the substance of cells, which are called mitochondria. Mitochondria are responsible for producing much of the energy that cells need in order to function normally.

1. What are the major findings on physical examination?
  - a. Short stature.
2. What is the age at diagnosis?
  - a. Patients have been diagnosed from birth to 7 years of age
  - b. The diagnosis is usually made in the first year of life.



3. What is the pattern of bone marrow failure?
  - a. The bone marrow fails to produce a specific type of white blood cell called “neutrophils.” When these cells are present in lower than normal numbers in the bloodstream, the condition is called “neutropenia.”
  - b. Low red cell count (anemia)
  - c. Low platelet count (platelets are the cells which help the blood to clot)
  - d. Patients may develop aplastic anemia when all 3 types of cells (red cells, white cells and platelets) are abnormally low because the bone marrow is not producing them.
  
4. What kinds of cancer develop?
  - a. No cancers have been reported in the medical literature to date in patients with Pearson Syndrome. However, persons with this disease may be at increased risk of leukemia.
  
5. How Pearson Syndrome is specifically diagnosed?
  - a. Blood counts are performed to detect the lower than normal numbers of particular cell types.
  - b. Bone marrow cells have holes (“vacuoles”) in them and an immature type of red cell containing excess iron deposits (“ring sideroblasts”) is detected.
  - c. Mutation analysis (genetic testing)
    - i. Laboratories can now identify the genetic “error” (mutation) in some patients, due to loss or deletion of some of the DNA from mitochondria.

### **Severe Congenital Neutropenia (SCN)**

SCN patients have very low white blood counts. Since white cells help the body to fight off infection, children with this disorder develop serious infections during infancy. The physical appearance is normal. The gene involved in many cases has been identified. It is called *ELA2*. Males and females are affected equally.

1. What are the major findings on physical examination?
  - a. These patients have normal physical examinations.
2. What is the age at diagnosis?
  - a. The diagnosis is usually made in the first year of life.
3. What is the pattern of bone marrow failure?
  - a. The bone marrow of patients with SCN fails to produce a specific type of white blood cell known as a “neutrophil”.
4. What specific kinds of cancer develop?
  - a. Leukemia (cancer of the blood and bone marrow)
5. How SCN is specifically diagnosed?
  - a. By doing a blood count and a bone marrow examination, doctors can detect the specific absence of neutrophil white cells.
  - b. Mutation analysis (genetic testing)
    - i. Laboratories can now identify the genetic “error” (mutation) in some patients, in a gene called *ELA2*.
    - ii. The disease usually occurs if a person has only one abnormal (mutant) gene. This form is thought to be inherited in an autosomal dominant manner.
    - iii. In some families, SCN occurs only if a person has **two** abnormal genes. This form of SCN is also known as Kostmann Syndrome, and it is inherited in an autosomal recessive manner. The gene which causes this form of SCN is *HAX1*.

### **Thrombocytopenia absent Radii (TAR)**

TAR patients are missing one of the two bones from each lower arm. The missing bone is called the radius, and it runs from the elbow to the wrist on the side of the thumb. The thumbs are not missing, as they are in some of the other bone marrow failure disorders (see Fanconi anemia, Diamond-Blackman (anemia)). Bruising is due to decreased production of platelets (the cells which help the blood to

clot) by the bone marrow and is usually apparent at birth. The gene for TAR has not been identified. Males and females are affected equally.

1. What are the major findings on physical examination?
  - a. The radius bone is missing from both lower arms.
  - b. The thumbs are present.
  - c. Patients may have small shoulders.
  - d. Patients may have abnormal knees such as bow legs or knock knees.
  
2. What is the age at diagnosis?
  - a. Patients are almost always diagnosed at birth.
3. What is the pattern of bone marrow failure?
  - a. The illness begins with a low platelet count.
  - b. Patients with TAR do not develop aplastic anemia (a condition seen in some of the other bone marrow failure disorders, when all 3 types of cells (red cells, white cells and platelets) are abnormally low because the bone marrow is not producing them).
4. What specific kinds of cancer develop?
  - a. Leukemia (cancer of the blood and bone marrow)
  - b. It is not yet clear whether patients with TAR are truly at increased risk of developing cancer.
5. How is TAR specifically diagnosed?
  - a. The diagnosis is made by physical examination, in which the radius bones in the arms are found to be missing.
  - b. A low platelet count
  - c. The specific gene or genes for TAR remain to be discovered.