**Fanconi anemia:** **A Comprehensive Overview of Genetics, Symptoms, and Disease Progression"**

**Abstract**

Fanconis anemia is an autosomal recessive disorder caused by biallelic mutation. The mutation mainly occur in proteins that are involved in cell cycle from DNA synthesis to its replication and its regeneration. The carrier frequency of disease is 1:300 of live birth in general population. The male to female ratio is 1.9:1. The chromosomal breakage test was considered as the gold standard for the diagnosis of disease but for the confirmation genetic analysis is mandatory because other syndrome can mimic with the fanconis anemia. The disease mainly characterized by physical abnormalities such as microcephaly, short stature with anomalies in skeletal development of both limbs, defective genitourinary system and abnormalities of eyes. Dysfunction of bone marrow can be observed from first decade of life which initially starts as thrombocytopenia or pancytopenia and later progresses to complete bone marrow failure. As patients enter their teenage years or young adulthood, they encounter a markedly higher risk of developing myelodysplastic syndrome and acute myeloid leukemia. To date there are 22 genes associated with fanconis anemia. The genetic foundation of FA, highlighting several FANC genes, particularly FANCA, FANCC, FANCG, and FANCD2, which are the most commonly mutated. There are distinct patterns of somatic chromosomal abnormalities seen in FA patients, especially unbalanced chromosomal translocations that result in partial duplications or deletions. The mechanisms underlying the hematopoietic defects and clonal evolution in FA are still largely unknown; however, comprehending these processes is essential for enhancing patient management and treatment.

**Keywords**: Fanconis anemia, bone marrow, chromosomal abnormalities, chromosomal translocations, pancytopenia and thrombocytopenia.

**Introduction**

First described in 1927 by Swiss pediatrician Guido Fanconis as familial, infantile anemia, Fanconis anemia (FA) is now known as a chromosomal instability syndrome with considerable clinical and genetic diversity. It involves mutations in at least 18 different genes that interact in a partially understood pathway related to DNA repair and oxidative stress management. The disorder leads to characteristic chromosomal abnormalities(1). FA is a rare autosomal (2) and 2% X-linked recessive disorder (3, 4). Mainly present as inherited bone marrow failure syndrome (iBMFS). Inherited bone marrow failure syndrome are mainly of three types, all three disease occur with mutation in functional or molecular pathway but result in bone marrow failure. For example defect in ribosomal biogenesis leads (Diamond-Blackfan anemia and the Shwachman-Diamond syndrome) also called as ribosomopathies while defect in telomere biology leads to telomeropathies and example include dyskeratosis congenita and its variant. Third category includes Fanconis anemia in which modification in DNA damage response (5, 6).

**History**

In 1927 Fanconis Anemia (FA) was noted in three siblings with same features of pancytopenia, hyperpigmentation and other congenital abnormalities then after year’s phenotype was describe by other reports. FA is linked to a range of congenital defects, such as increased pigmentation, microcephaly, short stature, convergent strabismus, and genital hypoplasia. Subsequent studies have highlighted a significant occurrence of skeletal abnormalities, especially in the forearm and hand. Estren and Dameshek (1947) noted instances of familial bone marrow failure in patients who did not exhibit congenital defects, suggesting a possible connection to FA (7).

**Incidence**

There are approximate 1-5 per million birth each year (8). It affects individuals across all ethnicities, with an incidence rate ranging from 1 in 160,000 to 360,000 live births. The carrier frequency of the condition is approximately 1 in 300 in the general population, but it is increased in specific ethnic groups, including South African Afrikaners, Spanish Gypsies, and Sub-Saharan Africans (9). There have been relatively few studies on the genetic basis of Fanconis anemia (FA) in South Asian and Middle Eastern populations (10). Previously it was not common in Pakistan but with increase rate of consanguineous marriages, the frequency of FA cases increased (11).

**Etiology**

FA gene are the most common genes that are mutated known as FANC other varieties which are mutated include FANCA, FANCC, FANCG and FANCD2 (12). Mainly mutation occur at the gene 16 and most of genes on autosomes except the FANCB which mainly located on x chromosome (13,14,15). The FANCB protein is an essential component of the FA core complex, which comprises products from six additional FANC genes as well as the FA-associated proteins FAAP100 and FAAP20. This complex plays a critical role in identifying stalled replication forks resulting from DNA interstrand crosslinks and is required for the monoubiquitination of DNA binding proteins (16). Fanconis Anemia (FA) proteins are believed to engage in interactions through a biochemical pathway or multimer complex. Specifically, FANCA and FANCC are thought to form a complex that moves to the nucleus, where they play a role in DNA replication, repair, and transcription (17). Main defect include impairment in the DNA repair pathway, mutation include point mutation, duplication, splicing and deletion (4, 18), there is hypersensitivity to agents that result in interstrand DNA crosslink agents mainly mitomycin C (MMC) and diepoxybutane (DEB) (19, 20,21).

**Association with other tumors**

 FA, first described in 1927, is recognized as a common pediatric bone marrow failure syndrome. It can progress to acute myeloid leukemia (AML) and solid tumors (22), particularly squamous cell carcinoma (SCC) affecting the aerodigestive and anogenital tract. (23, 24, 25).

The Fanconis anemia (FA) genes that predispose carriers to AML is the FANCA (26) while for breast and ovarian cancer are RAD51C and FANCM. RAD51C mutations have been associated with familial breast and ovarian cancer in monoallelic carriers and have a greater impact on ovarian cancer. In addition, RAD51C mutations have been associated with other tumors such as head and neck cancer. FANCM, originally associated with FA, These findings highlight the fundamental link between FA and familial breast and ovarian cancer predisposition (27). Biallelic pathogenic variants in FANCD1 (BRCA2) and FANCN (PALB2) increase the likelihood of developing embryonic cancers, such as Wilms tumor, neuroblastoma, and brain tumors, in patients with Fanconi anemia (FA), a risk that is not typically observed in other FA patients. From different studies in past it was suggested that relatives of FA have more chances to develop cancer in future due to heterozygous status (28).

**Association with Endocrinopathies;**

FA effect patients in embryonic life and postnatally. In fetus FA genes decrease the growth and development markedly so low birth weight with height at 5th centile can easily appreciated in FA patients while study conducted in 54 FA patients showed that in post-natal life FA altered growth hormone response to 44% and also 36% decrease thyroid response i.e. hypothyroidism. Other than that level of insulin were also diminished with altered glucose level (29).

**Clinical presentation**

The classical features of fanconis anemia include physical deformities, pancytopenia with increased risk of malignancies especially of head and neck and solid tumors (30, 31).

Individuals with (FA) generally have an average lifespan of 20 to 30 years, although some may live into their 40s and 50s. The primary symptoms include hematological malignancies, especially bone marrow failure (BMF), which impacts 75–90% of patients during their first decade of life (17). Most of the children of FA presents at the age of 7 years with clinical symptoms of dyspnea, chest pain, vertigo and fatigue with signs of blood disorder like epistaxis, easy to bruise, small petechial hemorrhages and uninterrupted bleeding from wound site. These are the common feature due to thrombocytopenia (29).

Majority of FA patients presents with physical abnormalities that leads to functional defects i.e. hypo or hyperpigmentation, microcephaly, growth retardation with congenital deformities of upper limb especially defects of thumb, triangular face, micropthalmia and cardiac and renal malformations (32). FA patient mainly presents with life threatening bone marrow failure leads to aplastic anemia (33, 34, 35). Other than the prominent features many patients also come with complain of infertility but there is delay in diagnosis of some patients because they do not present with classical characteristics of FA (36).

**Diagnosis**

Chromosomal fragility tests, particularly mitomycin C (MMC) and bleomycin tests, are utilized as a cellular marker for diagnosing and also distinguish between Fanconi anemia (FA) and aplastic anemia (AA). These tests assess the sensitivity of patients' cells to DNA-damaging agents, revealing specific chromosomal abnormalities associated with FA. The hypersensitivity of cells affected by FA to clastogens is considered a more dependable diagnostic marker. Individuals with FA have significantly higher rates of chromosomal breakage compared to those with AA, confirming the utility of these tests as important diagnostic tools. But chromosomal breakage test can give false positive result Evaluating the cell cycle profile of peripheral blood lymphocytes is useful for diagnosing Fanconis anemia, as FA cells demonstrate a marked increase in the G2/M phase (indicating 4N DNA content) either prior to or following treatment with DNA interstrand crosslinking agents. The definitive diagnostic method is the complementation test, commonly referred to as FA subtyping. In this procedure, FA cells derived from patients are transduced with retroviruses carrying cDNAs for different FA subtypes. When the correct FA complementation group (FANC) cDNA is effectively introduced, it can correct the cellular phenotypes associated with FA, such as chromosomal abnormalities and heightened sensitivity to DNA ICLs (36, 37). By providing accurate diagnoses of FA, these tests can guide treatment approaches, ultimately improving patient care and outcomes (38, 15).

**Management**

Modern management of Fanconis anemia (FA) involves comprehensive monitoring and treatment plans that begin at diagnosis and continue throughout the patient's life. Treatment options for bone marrow failure (BMF) include androgens, which can boost red blood cell and platelet counts but may cause long-term side effects. Additionally, hematopoietic growth factors like G-CSF or GM-CSF are used to improve neutrophil counts. The most effective treatment for BMF is hematopoietic stem cell (HSC) transplantation, preferably from a histocompatible sibling donor, and it should be carried out before hematopoietic defects develop (17). Hematopoietic stem cell transplantation (HSCT) is the main treatment option for FA bone marrow failure, with improved results over the past two decades. HSCT is most effective when performed under optimal conditions before the development of severe cytopenias, transfusion dependence, clonal development, absence of previous androgen treatment, normal liver function, and fewer congenital malformations or myelodysplasia/acute myeloid leukemia (39, 40). Patients of FA usually presents with other somatic abnormalities i.e. physical deformity that require specific management. Moreover in FA malignancies are more common either of hematological or non-hematological type that needs a timely diagnosis and treatment of malignancy and its complications (41). An increased risk of secondary neoplasms (SN) exceeding 15% has been noted more than 20 years following hematopoietic cell transplantation (HCT), along with related mortality. This emphasizes the critical necessity for careful monitoring to ensure the early detection of secondary neoplasms in transplant recipients (42).

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