REVIEW ARTICLE

Fanconi Anemia (FA): A Comprehensive Overview of Genetics, Symptoms, and Disease Progression

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Abstract

Fanconi anemia (FA) is an autosomal recessive disease caused by a biallelic mutation which mainly occurs in proteins involved in the cell cycle, from DNA synthesis to replication and regeneration. The carrier frequency of disease is 1:300 of live births in the general population. The male-to-female ratio is 1.9:1. The chromosomal breakage test was considered the gold standard for the diagnosis of the disease but for the confirmation genetic analysis is mandatory because other syndrome can mimic with the FA. The disease is mainly characterized by physical abnormalities such as microcephaly, short stature with skeletal anomalies of both limbs, defective genitourinary system and abnormalities of the eyes. Bone marrow dysfunction is usually observed from the first decade of life which initially starts as thrombocytopenia or pancytopenia and later progresses to bone marrow failure. As patients enter their teenage or adulthood, they encounter a high risk of myelodysplastic syndrome and acute myeloid leukemia. To date, 22 genes are associated with FA. The genetic foundation of FA highlights 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 duplication or deletions. The mechanisms underlying the hematopoietic defects and clonal evolution in FA are still largely unknown; however, understanding these processes is essential for enhancing patient management and treatment.

Keywords: *Fanconi anemia (FA), bone marrow, chromosomal abnormalities, chromosomal translocations, pancytopenia and thrombocytopenia.*

INTRODUCTION

First described in 1927 by Swiss pediatrician Guido Fanconi as familial, infantile anemia, Fanconi anemia (FA) is now known as a chromosomal instability syndrome with considerable clinical and genetic diversity. It involves mutations in at least 22 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], present as inherited bone marrow failure syndrome (iBMFS). Inherited bone marrow failure syndrome is mainly of three types, all three diseases occur with a mutation in functional or molecular pathways but result in bone marrow failure. For example, defects in ribosomal biogenesis lead (Diamond-Blackfan anemia and the Shwachman-Diamond syndrome) also called ribosomopathies while defect in telomere biology leads to telomeropathies *i.e.* dyskeratosis congenital and it's variant. The third category includes FA which modification in DNA damage response [5, 6].

HISTORY

In 1927 FA was noted in three siblings with the same features of pancytopenia, hyperpigmentation and other congenital abnormalities. FA is linked to a range of congenital defects, such as increased pigmentation, microcephaly, short stature, convergent strabismus, and genital hypoplasia. Subsequent studies have emphasized 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 approximately 1-5 per million births 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]. Few studies published on the genetic basis of FA in South Asian and Middle Eastern populations [10]. In Pakistan, consanguineous marriages show an increase in cases of FA [11].

ETIOLOGY

FA genes 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 occurs at gene 16 and most of the genes on autosomes except the FANCB which is mainly located on the X chromosome [13-15]. 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

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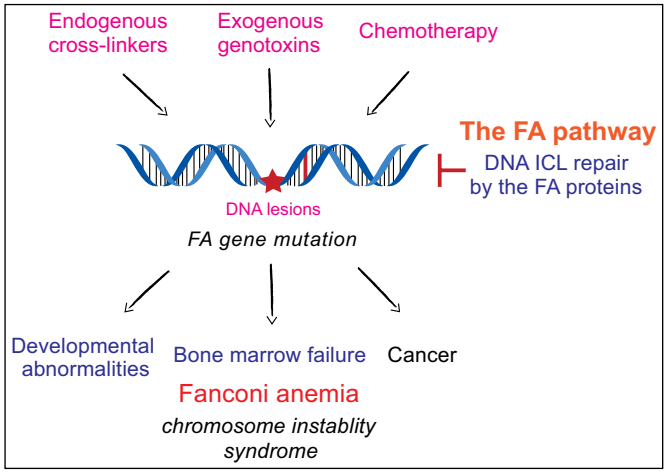

Fig. (1): Mutation of FA genes involved in development of disease [17].

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]. FA proteins are believed to engage in interactions through a biochemical pathway or multimer complex. 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] (**Fig. 1**).

Main defects include impairment in the DNA repair pathway, mutation including 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) [19-21].

ASSOCIATION WITH OTHER TUMORS

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

Fanconi anemia (FA) genes that predispose carriers to AML are the FANCA [26] while for breast and ovarian cancer are RAD51C and FANCM. RAD51C mutations have been associated with familial breast and ovarian cancer. And also associated with other tumours 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 strains in FANCD1 (BRCA2) and FANCN (PALB2) increase the likelihood of developing embryonic cancers, such as Wilms tumour, neuroblastoma, and brain tumours, in patients with FA, a risk that is not typically observed in other FA patients. Siblings 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 postnatal life. In fetuses, FA genes decrease growth and development markedly, and low birth weight with height at the 5th centile can easily appreciated in FA patients. A study conducted on 54 FA patients showed that post-natal life decreased growth hormone response by 44% and thyroid response by 36%. Levels of insulin were also diminished with altered glucose levels [29].

CLINICAL PRESENTATION

The classical features of FA include physical deformities, and pancytopenia with an increased risk of malignancies especially of head and neck and solid tumours [4, 30].

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 present 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 the wound site. These are the common features of thrombocytopenia [29].

The majority of FA patients present with physical abnormalities that leads to functional defects *i.e.* hypo or hyperpigmentation, microcephaly, growth retardation with congenital deformities of the upper limb especially defects of thumb, triangular face, micropthalmia and cardiac and renal malformations [31]. FA patients are mainly present with life-threatening bone marrow failure that leads to aplastic anemia [32-34]. Many patients also come with complaints of infertility but there is a delay in diagnosis because they do not present with classical characteristics of FA [35].

DIAGNOSIS

Chromosomal fragility tests, particularly mitomycin C (MMC) and bleomycin tests are utilized as cellular markers for diagnosing and also distinguishing between 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 results Evaluating the cell cycle profile of peripheral blood lymphocytes is useful for diagnosing FA, as FA cells demonstrate a marked increase in the G2/M phase (indicating 4N DNA content) either before 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 [35, 36]. By providing accurate diagnoses of FA, these tests can guide treatment approaches, ultimately improving patient care and outcomes [15, 37].

MANAGEMENT

Modern management of 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. 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 care 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, and clonal development, absence of previous androgen treatment, normal liver function, and fewer congenital malformations or myelodysplasia/ acute myeloid leukemia [38, 39]. Patients of FA usually present 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 need a timely diagnosis and treatment of malignancy and its complications [40]. An increased risk of secondary neoplasms (SN) exceeding 15% has been noted for 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 [41]. Hematopoietic stem cells (HSCs) have a remarkable ability to regenerate, which can help restore normal blood function in people with FA after genetic correction. In FA patients, the presence of mosaicism allows the corrected stem cells to thrive and outcompete the faulty ones, making gene therapy (GT) a hopeful treatment option. This approach often involves using viruses, like adenoviruses or retroviruses, to deliver healthy copies of specific FA genes, such as FANCC, into the HSCs. While there are concerns about the potential risks of gamma-retroviruses, recent advancements in lentiviral (LV) vectors have shown they can be safe and effective, providing the necessary support to correct the blood-forming cells in FA patients [42].

CLINICAL TRIAL

From different studies, it was found that significant effects of gene therapy (GT) on people living with (FA). In an earlier clinical trial with four patients, it was found that three of them went through several rounds of gene transfer using retroviral vectors to introduce normal FANCC genes into their hematopoietic stem cells (HSCs). This trial showed a significant increase in HSC colonies in the lab and a temporary improvement in bone marrow health. Most of the clinical trials for FA, both past and present, have focused on using retroviral methods, especially lentiviral vectors. At the same time, there have been exciting advancements in gene editing techniques. These techniques work by creating specific breaks in DNA using special enzymes and then repairing those breaks through methods like non-homologous end joining (NHEJ) or homology-dependent repair [42]. Another study using lentiviral vectors has shown a fundamental promise in altering patients' own CD34+ hematopoietic stem and progenitor cells. This is helpful in both clinical trials (phase I and II) [43].

CONCLUSION

FA is a rare genetic condition that people inherit in an autosomal recessive manner, meaning both parents must pass on the faulty gene for a child to be affected. This disorder disrupts the body's ability to repair DNA, leading to problems with chromosomes. Individuals with FA often experience serious health challenges, including bone marrow failure and low blood cell counts, which can result in symptoms like fatigue and increased risk of infections. They may also have noticeable physical features, such as smaller head size (microcephaly) and skeletal abnormalities.

While the average lifespan for someone with FA is around 20 to 30 years, some individuals manage to live into their 40s and 50s. Diagnosing FA usually involves specific tests that check for chromosomal damage and genetic testing to identify mutations in certain FANC genes. As people with FA age, they face a greater risk of developing conditions like myelodysplastic syndromes and acute myeloid leukemia. This makes early diagnosis and proactive management essential for improving their quality of life and health outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Dr. Shahameen Aqeel: Abstract and title
Dr. Areeba Aqeel: Formatting
Dr. Shahjabeen Khan: Main correction in the article
Dr. Sana Kashif: Management
Dr. Fozia Shamshad: Clinical trials

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