ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

Fanconi Anemia a Rare Disease*

Manoj Kumar S*; Anagha S; Aamina Haneef; Reshma P Varghese; Kezia K Sabu; Sreenivasan A
Department of Pharmacy Practice, Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Tamil Nadu-638183, India

Corresponding author,
MANOJ KUMAR S
Doctor of Pharmacy
Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Tamil Nadu-638183, India

Abstract:- Fanconi anemia (FA) is a genetically and phenotypically recessive autosomal illness. Fanconi anemia (FA), a rare genetic illness, is currently receiving more attention from hematologists, cancer biologists, and fundamental scientists studying DNA repair and ubiquitin biology. Chromosome instability, progressive bone marrow failure, cancer susceptibility, and several other congenital anomalies are its defining characteristics. All three blood cell lines are included. This is a fatal illness that typically strikes children under the age of five.

One of the fastest-growing fields of medical study is FA. The discovery of 15 distinct FA genes and the clarification of the FA molecular pathways have contributed to our knowledge of the pathogenic mechanism and, in many cases, the development of treatment guidelines.

Because FA possesses distinct traits in many different biological areas, investigations on FA provided significant material for studies on malignancies. Research has demonstrated a genetic relationship between FA and cancer, showing that both cancer genes and FA genes are present in malignancies. FA is therefore identified as a prototypical illness for the comprehension of aging and cancer.

Here we review the incidence of FA, Genetics, Pathophysiology, impact of FA, Identification of FA genes and delineation of FA pathways, Symptoms and indication, Diagnosis, Management, Complication and Prevention, and patient education about FA.

Keywords:- *Fanconi Anemia, Bone Marrow Failure, Hematological Abnormalities, Pancytopenia, Aplastic Anemia.*

I. INTRODUCTION

A genetic instability disease called Fanconi anemia (FA) is linked to birth defects, bone marrow failure (BMF), and a higher risk of malignancy. Because Fanconi anemia is a rare autosomal recessive genetic disorder affecting all three blood cell lines, where homozygous or heterozygous mutations result in pathogenic alleles, including point mutations, duplications, splicing defects, and deletions, it is the most common cause of inherited bone marrow failure [1]. This is the most prevalent inherited form of bone marrow failure syndrome, however, it falls within the uncommon disease group with a prevalence of 1 in 160,000 (www.orpha.net) [2].

In 1927, Swiss pediatrician Guido Fanconi identified and classified FA as a disease based on the characteristics of three brothers who had a particular mix of bone marrow failure and physical anomalies, including short height, hypogonadism, and hyperpigmentation. Many FA cases have now been reported, all of which show progressive bone marrow loss rather than congenital abnormalities [3]. In 1964, a lab discovery of elevated spontaneous chromosomal fragility in FA was published [4] In 1967, FA was identified as the initial etiology of juvenile leukemia[5].

Because the cells cannot repair themselves, the genetic abnormalities causing Fanconi anemia led to a build-up of chromosomal damage [6][7]. Fanconi anemia proteins normally repair DNA interstrand crosslinks (ICLs) to preserve genomic integrity and replication potential. ICLs preserve DNA integrity by preventing DNA strand separation. Due to these genetic mutations in the Fanconi anemia pathway, cells become unable to repair DNA damage correctly, which leads to genomic instability, pancytopenia, and an increased vulnerability to cytotoxic agents, UV radiation, spontaneous deformation, and a higher risk of developing cancers. Furthermore, practically every organ in the body is impacted by Fanconi anemia [8]. The most common FA genes are FANCA, FANCC, FANCG, and FANCD2, which are the genes that have been discovered to be mutated in FA patients [9]. All other FANC genes are autosomic, and the illness is recessive, except for the extremely uncommon FANCB, which is found on the X

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

chromosome. When it comes to FA, there are usually multiple age-related clinical stages [10][11].

Another theory regarding fanconi anemia is that it is an inherited type of aplastic anemia.The scientific understanding of chromosomal fragility illnesses and other bone marrow failure syndromes has improved with extensive research on Fanconi anemia. Fatigue, dizziness, chest pain, and shortness of breath are typical clinical signs of Fanconi anemia. Moreover, thrombocytopenia frequently results in a clinical history of epistaxis, petechiae, and profuse bleeding from a wound site. The ailment is primarily linked to further congenital malformations and is typically more prevalent in young age, with an average diagnostic age of 7 years. Patients with Fanconi anemia are more likely to have structural extremities abnormalities found during physical examinations. Additionally, the condition may make individuals more susceptible to solid and hematologic tumor growth. The pancytopenia characteristic with Fanconi anemia is typically observed in serum laboratory assays that show a reduction in leukocytes, platelets, and red blood cells (RBCs), among other blood cell types [12].

Early detection of FA influences the prognosis by enabling the forecast of potential consequences. Chromosome breakage testing is used to confirm the diagnosis, which can be made early based on clinical suspicions and positive results from genetic analysis. Other diagnostic techniques include gene sequencing studies using next-generation sequencing (NGS), western blotting, and multiplex ligation-dependent probe amplification (MLPA) [13][14].

There are numerous synonyms for FA, including pre-malignant disorder, chromosome break up syndrome, Fanconi pancytopenia, inherited aplastic anemia, inherited pancytopenia, constitutional aplastic anemia, DNA repair disorder and inherited bone marrow failure syndrome. FA is the most extensively used and broadly accepted name among these synonyms. It is important to distinguish it from the kidney disease Fanconi syndrome.

II. INCIDENCE OF FANCONI ANEMIA

Every race and ethnic group is affected by FA, which is predicted to affect 1 in 160,000–360,000 live births in the general population. However, because of founder effects, the frequency of FA is significantly higher in some ethnic groups [15][16][17].

Globally, the carrier frequency of FA in the general population is 1:300. However, among sub-Saharan Blacks, Spanish Gypsies, and Afrikaners in South Africa, the carrier frequency is less than 1 in 100, while in the United States, it is 1:181[18][19].

FA patients are nearly one to one in terms of gender. Eight years old is the median age at which anemia manifests itself clinically. The life duration ranges from 0 to 50 years (mean about 20 years old), the median diagnostic age is approximately 10 years (often between 2 and 15 years), and the most prevalent cause of death is bone marrow failure [20].

III. GENETICS

When the X chromosome's FANCB gene is mutated, the condition is inherited autosomally recessive; however, when the FANCR gene is mutated, it is inherited autosomally dominantly [21][22]. When a DNA sequence is linked to chromosomal breakage in at least one patient after being exposed to DNA cross-linking agents (like MMC and DEB), and the breakage is repaired by complementation with the wild-type copy of the mutant alleles, the sequence is considered to be an FA gene [23]. Thus far, 21 genes and one x-linked gene have been revealed to have biallelic mutations connected to the FA phenotype [23][24]. The genes that correspond with distinct complementation groups in FA are implicated in the DNA damage repair pathway of FA/BRCA and are crucial in initiating an immune response against DNA alkylating chemicals[25]. It has been discovered that FANCA, FANCG, and FANCC are prevalent FA complementation groups [26]. The FANCA gene mutation predominates in between 60 and 70 percent of patients with FA. These alterations could be null, massive deletions, insertions, or deletions that could result in an early termination [27].

IV. PATHOPHYSIOLOGY OF FA

FA patients have a variety of congenital abnormalities, while between 25% and 40% of them are physically normal [28]. Because the cell is unable to heal itself, Fanconi anemia is characterized by chromosomal damage [6][7]. The whole Fanconi anemia pathway becomes defective when there are biallelic mutations in the genes linked to the Fanconi anemia core complex. More than 80% of cases are caused by biallelic mutations in the FANCA, FANCC, and FANCG genes [29].It is believed that CD34+ stem cell death is the cause of bone marrow failure in Fanconi anemia patients. Homologous recombination, nucleotide excision repair, mutagenesis translational synthesis, and alternate end joining are among the main DNA repair pathways that are interfered with. Stabilizing replicative forks and controlling cytokines are two aspects of replication processes.

Maintaining genomic integrity and replicative capability is the goal of Fanconi anemia proteins. Several Fanconi anemia proteins preserve genomic stability by fixing DNA interstrand cross-links (ICLs). Integrity-preserving loops (ICLs) stop DNA strand separation. DNA damage cannot be correctly repaired by cells due to genetic abnormalities in the Fanconi anemia pathway. This leads to genomic instability, pancytopenia, and an increased vulnerability to cytotoxic chemicals, UV radiation, spontaneous deformation, and a predisposition to cancers. Research has demonstrated that FANCA mutations affecting exons 27 to 30 are more prevalent in solid tumors, such as head and neck squamous cell carcinomas [30].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

The Fanconi anemia genes encode ubiquitin ligase, monoubiquitinated protein, helicase, and proteins that predispose to breast and ovarian cancer. These proteins are in charge of DNA repair and defense against external stressors that damage DNA. Certain Fanconi anemia proteins, like FANCD1, function in the Fanconi anemia-BRCA network and are comparable to the BRCA2 protein. Ataxia-telangiectasia, Bloom syndrome, breast and ovarian cancer, and other unusual genetic diseases are caused by an interacting network between these Fanconi anemia proteins and other proteins [31][32][33]. These proteins involved in Fanconi anemia serve a variety of additional purposes. The Fanconi anemia pathway uses FANC genes and their products to preserve genomic integrity. Fanconi cells exhibit heightened sensitivity to crosslinking agents, such as cisplatin, diepoxybutane, and mitomycin C. Other stress response pathways involve proteins associated with Fanconi anemia. Oxidative damage results from impacted cells' incapacity to tolerate typical oxidative stress and oxygen-free radicals [34].

V. IMPACT OF FANCONI ANEMIA

The majority of cases of FA occur in children, and almost half of them have congenital skeletal abnormalities, most commonly affecting the thumb and forearm. Thumbs are typically missing, hypoplastic, or undersized. There's also a chance that the forearm's radius is nonexistent or reduced [35]. Endocrine problems are prevalent among FA persons. About half of FA people are short in stature, which is associated with hyperthyroidism and insufficient growth hormone synthesis. Certain FA individuals are of normal height and may not exhibit a clear impairment in growth hormone production. FA is also linked to improper metabolism of insulin or glucose. Those with FA typically have higher serum insulin levels than those with diabetes, which is the opposite of decreased insulin. It is estimated that 8% of people with FA have diabetes, and up to 72% have high insulin [36][37]. Furthermore, FA is also linked to osteoporosis [36][37][38][39].

The most common pathologic symptom of FA is hematologic abnormalities. During the first decade of life, between 75 to 90 percent of FA patients experience mild to severe bone marrow failure [40][41]. Furthermore, the majority of FA persons experience various degrees of blood illness, such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or aplastic anemia. With a median age of onset of 14 years, the risk of developing AML is around 800-fold higher than that of the general population. Certain chromosomal abnormalities (such as gain of 1q23-32 or 3q26) were found to be a prevalent pattern in FA patients with MDS or AML in recent investigations, suggesting that these abnormalities can be helpful prognostic indicators [42][43].

Even though FA is primarily a pediatric illness, adult FA patients (>18 years of age) now make up a larger percentage of FA patients because of better adult diagnostic testing and better management of younger FA patients. The possibility of malignancy is a significant health concern for adult FA patients [44]. Apart from hematologic cancers, people with FA also have much-increased incidences of solid tumors, especially squamous cell carcinomas (SCCs) of the head and neck and cervical/gynecological cancers [45].

FA patients show other clinical issues, such as hearing loss and ear abnormalities as well as decreased fertility, in addition to the hematological abnormalities and higher cancer susceptibility [35]. For male FA patients, a lower sperm count is linked to the condition, while for female patients, an earlier menopause [46]. Several investigations using knockout mice models of Fanca, Fancc, Fancg, and Fancd2 demonstrated marked hypogonadism and poor fertility, with females more severely affected than males, which is consistent with the reduced fertility in FA patients [47][48].

VI. IDENTIFICATION OF FA GENES AND DELINEATION OF FA PATHWAYS

FA is brought on by mutations in the FA genes that code for the synthesis of proteins that help shield and repair damaged DNA. FA is categorized into 15 distinct complementation groups. These 15 corresponding FA genes have been found and given names in alphabetical order, ranging from A to P. They are dispersed extensively across 11 distinct chromosomes in the human genome [49][50] Only one of the fifteen FA genes—FANCB—is X-linked and sex chromosome recessive, while the other fourteen are autosomal recessive [51].

Approximately 90% of all mutant FA genes are of the FANCA, FANCG, and FANCC kinds. Probably, there are still unidentified uncommon complementation groups. About 60–70% of all mutant FA genes are caused by mutations in the FANCA gene, yet this complementation group is overrepresented in specific geographical areas, such as Mediterranean nations like Spain, where 80% of patients have FANCA mutations. FANCA has been reported to have a variety of mutations, including missense, nonsense, splicing, micro-deletions, micro-insertions, and duplications [52]. Approximately 15% of all altered FA genes are caused by mutations in the FANCC gene. Since its discovery in 1992, the expression, subcellular localization, interactions with other proteins, and gain or loss of function of the FANCC gene have all been the subject of much research. This one is one of the larger FA genes, measuring over 218 kb and encoding a 63 kDa protein. Research revealed that FANCC is involved in cytokine signaling and the growth of hematopoietic stem cells and germ cells[53].

Of the 15 altered FA genes, mutations in FANCG account for around 10% of the cases. Compared to other mutations, FANCG mutations were often more severe when it came to cytopenia and leukemia incidence; null mutations also produced an altered protein. Compared to FANCA and FANCC, the relative risk of bone marrow failure is higher in FANCG [54]. Multiple FA pathways are comprised of the 15 FA gene protein products. The FA nuclear core protein complex is the protein product of FANCA, FANCB,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM. In response to DNA damage during replication, another FA pathway made up of FANCD2 and FANCI can activate this route [55]. Among these, helicase, monoubiquitinated proteins, and ubiquitin ligase are crucial for DNA repair and maintaining genomic integrity. Any one of the 15 gene mutations can lead to errors in the body's reaction to DNA damage and improper repair, which can ultimately result in FA disease.

The severity and clinical course of FA might differ between families as well as within them. Because there are so many variables influencing the interplay between genes and environment, it is unknown to what extent genotype and illness phenotype are correlated.

VII. SYMPTOMS AND INDICATIONS ASSOCIATED WITH FANCONI ANEMIA

By the age of 4 to 7 years old, signs and symptoms, mostly hematological abnormalities, begin to appear. One example of this is pancytopenia, which is characterized by a decrease in the quantity of platelets, red blood cells, and white blood cells. Thus, urogenital anomalies, pancytopenia, hyperpigmentation, skeletal deformities, central nervous system, auditory, renal, ophthalmic, and familial incidence are the key criteria for diagnosing FA. It has been noted that probands have a higher incidence of congenital defects than their affected sibling. A proband is the member of the family who is initially impacted and who provides the basis for the genetic study within that family[56]. Typical symptoms of FA include fatigue, shortness of breath, dizziness, and chest pain. Patients report thrombocytopenia-related petechiae, epistaxis, and uncontrollably bleeding wounds. Fever and flu-like symptoms are common, and leukopenia increases the risk of infection.

Birth abnormalities are seen in about 75% of FA patients. The child may present with low height and café-au-lait spots (an region of skin hyperpigmentation) in about 50% of the instances[57]. Additional anomalies related to FA in the extremities include dysplastic ulna, hypoplastic or missing radii, hypoplastic thumb (radial ray defect), and hip dislocation in the lower extremity and club foot, polydactyly, and thigh osteoma in the upper extremity. Additional anomalies of the skeleton include micrognathia, scoliosis, aberrant ribs, spina bifida, webbed and short necks, microcephaly and hydrocephaly, and frontal bossing. Among the gastrointestinal anomalies seen in FA include tracheoesophageal fistula, imperforate anus, umbilical hernia, and Meckel's diverticulum. Anomalous gastrointestinal conditions are less frequent.

Pancytopenia can cause petechiae, pallor, bruises, and cold hands and feet as physical symptoms. Between the ages of 2 and 13, children with FA experience pancytopenia and bone marrow aplasia. Certain patients might exhibit these symptoms later in life, perhaps even in their adolescent or beyond. The majority of FA patients eventually experience myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)[58][59][60]. As a result, these patients need to have routine follow-up. These people have an extremely high chance of both hepatic adenoma and hepatocellular cancer[61][62]. The European Fanconi Anemia Research Group published an investigation which revealed that 8 and 9% of the patients diagnosed with FA went on to develop MDS and AML, respectively. AML/MDS was the first hematological abnormality found in some of the patients, while a small number of individuals developed AML/MDS after bone marrow aplasia. Patients in the former group presented much younger than in the latter. In FA individuals with AML/MDS, cytogenetic abnormalities usually occur, including deletions of 5q, 7q, 20q, trisomy 8, monosomy 7, and chromosome 1[60].

Growth abnormalities, such as short height, are frequently linked to hormone deficits, including pituitary hypofunction, hypogonadism, insulin resistance, and growth hormone deficiency. There are cases of hypogonadism in both sexes. A hypothalamic-pituitary malfunction may be the underlying cause of the aberrant growth hormone secretion. Therefore, it is recommended that all children have endocrine evaluation at a young age to correct growth and thyroid hormone insufficiency and ultimately improve quality of life and final height [63].

VIII. DIAGNOSIS AND LABORATORY TESTING STRATEGIES FOR FA

A. T-Lymphocyte Chromosomal Fragility Testing

Spontaneous chromosomal breakage was first proposed as a potential marker for FA, however, subsequent research revealed inconsistent results [4]. The novel technique known as "chromosomal fragility testing" was first reported by Cervenka et al. in 1981[64]and Auerbach in 1993[65]. It involves the use of two clastogenic chemicals, diepoxybutane (DEB) and mitomycin C (MMC). The idea behind this technique is to expose the hyposensitive FA cells in the cell culture—typically T lymphocytes from peripheral blood—to DEB and MMC. Then, the chromosomal aberrations, breaks, and rearrangements (radial exchanges) are examined. A total of fifty metaphase cells are analyzed and graded for chromosomal breakages in comparison to controls under the same age and sex conditions. If the overall chromosomal breakage is greater than 10 times compared to the control, it is positive.

This technique often distinguishes between FA and non-FA cells. It is referred to as the "Gold standard" because of its simplicity, reproducibility, dependability, and sensitivity when compared to other testing techniques for the diagnosis of FA, such as the immunoblot assay of FANCD2 protein monoubiquitination, which has the drawback of potentially missing rare types of FA, and the cell cycle arrest assay, which uses skin fibroblasts exposed to MMC before being detected by flow cytometry [66][67] Despite being time-consuming and requiring specialized people, chromosomal fragility testing has been the most commonly used procedure as the first line laboratory screen for FA in the past 20 years. It has been suggested that even in patients who do not have anemia but have congenital abnormalities, chromosomal fragility testing ought to be performed more

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

frequently. This approach has two drawbacks: (I) it cannot identify the carriers, and (II) in somatic mosaic cases of FA, it is frequently inconclusive. Furthermore, if the test subject who was referred for the exclusion of FA is receiving chemotherapy or radiation therapy within a specific time frame, false positive test findings may occur.

B. Skin Fibroblast Testing for the Suspected Cases in Somatic Mosaicism

A study utilizing lymphocytes to test for FA revealed that 15-20% of patients had limited response to DEB and MMC because of mosaicism [68].The existence of two genetically different populations of lymphocytes within a particular organism is known as mosaicism. Among individuals with FA, it is rather typical for one to have elevated sensitivity to DEB/MMC while the other displays normal levels of chromosomal breakage in response to DEB/MMC. When there are strong clinical signs of FA but low chromosomal fragility testing results, cultured skin fibroblasts are required for additional testing using DEB and MMC or other techniques in such suspected FA cases with somatic mosaicism.

C. Determination of FA Complementation Groups

The next step is to identify the FA complementation group once FA has been confirmed by chromosomal fragility testing. Complementation group testing is performed to categorize FA patients based on the particular gene abnormalities causing FA. In order to determine which FA complementation group to use for further DNA sequencing of gene mutations, the complementation group testing method involves infecting test FA cells with a retrovirus that contains cDNA from an FA gene[69].Living cells from FA patients are needed for this assay (either skin fibroblast for mosaic or lymphocyte for non-mosaic).

D. Mutation Analysis

Determining the precise gene mutations in each case is crucial, since it affects the disease's severity and the likelihood of acquiring aplastic anemia or cancers associated with the complementation groups. Following confirmation by the primary complementation group result, the purpose of mutation analysis is to pinpoint the precise gene alterations from the proband.

Because there are at least 15 altered genes involved, traditional molecular genetic testing used to be difficult and time-consuming. It also required several procedures, such as DNA amplification, sequencing, and significant deletion identification. Typically, these tests must be carried out in facilities with specialized training.

The criteria and instructions for mutation analysis are provided by the International FA Research Fund[70].

- *Sequence Analysis for Mutations*

Sequence analysis is applied to all known genes related to familial arthritis. The amount of genes that need to be analyzed, the numerous mutations that could occur in each gene, the occurrence of significant insertions or deletions in some genes, and the size of many FA-related genes make sequence analysis difficult**.** By sequencing the appropriate gene, the causative mutation can be identified if the complementation group has been identified. Complementation A patients with several hundred mutations make up the majority of FA patients globally.

- *Deletion/Duplication Analysis*

In each suspected case of familial anomalies, deletion/duplication analysis is also utilized to identify deletions of one or more exons, or of a whole gene. The next generation sequencing technology has made it possible to conduct mutation analysis for FA genes without the need for living cells, which is necessary for complementation group testing, making molecular diagnostics for FA gene investigations more efficient and quicker[71].

IX. MANAGEMENT OF FANCONI ANEMIA

Therapy for bone marrow failure. In patients with FA, bone marrow failure usually appears in the first decade of life[72].

For some FA patients, androgen therapy is an effective treatment for bone marrow failure. Patients with FA have found success in treating their hematological abnormalities using synthetic androgens such as danazol and oxymetholon[73].

Though hirsutism and an increased risk of liver tumors are among the negative effects of long-term androgen use. While androgens raise platelet and red blood cell numbers, [74]. There is confusion over the precise role that androgens play in the hematological system. The neutrophil counts in FA have been demonstrated to be improved by hematopoietic growth factors, such as G-CSF and GM-CSF[75].

For FA patients with bone marrow failure, HCT is still the recommended course of treatment. Due to the underlying DNA repair deficiency in FA, the transplantation process can be extremely hazardous due to intensive chemotherapy and radiation. If a sibling donor transplant is done early (i.e., before leukemia or MDS develops), it continues to be the best treatment for FA and has the best results[72][76]. However, chemoradiation-induced physical harm (such as pulmonary and renal toxicity and veno-occlusive disease), graft-versus-host disease (GvHD), immunological damage, sterility, and endocrinopathies are among the many difficulties that transplant survivors face. Modifications to the HCT conditioning protocol, such as the use of an immunosuppressive regimen based on fludarabine and lower doses of cyclophosphamide (an alkylating drug), or nonirradiation, keep these issues under control while keeping enough engraftment rates[77][78][79][80] .

Since the majority of FA patients lack a sibling who is histocompatible, some families have turned to preimplantation genetic diagnosis (PGD) in an attempt to find a compatible donor[81].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

Higher risk of complications and worse survival rate are linked to HCT from alternate (unrelated or HLA mismatched) donors. Yet, since Gluckman and colleagues first reported the results of alternate-donor HCT for FA patients in 1995, the survival percentage has gradually increased[82].

Lately, the conditioning regimen's irradiation has been reduced, which has limited harmful effects and increased the survival rates of alternate-donor HCT.[80] .Although HCT is very effective in prolonging the life expectancy of patients with FA, it is now more crucial to manage the long-term consequences of HCT. Furthermore, nonhematopoietic FA problems such as elevated cancer susceptibility are not addressed by HCT.

Genetic treatment. Interest in gene therapy for FA has increased recently. FA is a prime example of an illness that would benefit greatly from gene therapy. It is generally simple to subtype FA patients, which enables the identification of the mutant FA gene and the production of lentiviral or retroviral vectors that convey the wild-type cDNA to complement cells. In vivo, transduced and cDNA-complemented cells ought to exhibit a definite selection advantage over native bone marrow cells. Moreover, gene therapy offers a way to produce autologous donor cells. But a number of technological challenges have made effective gene therapy for FA more difficult. Initially, FA patients do not have enough HSCs for ex vivo transduction. Thus, early in the FA patient's life, bone marrow should be extracted and preserved. To grow FA bone marrow cells ex vivo, new techniques are required; these may involve the utilization of HOXB4 and DELTA-1[83].

Second, there has to be an increase in viral transduction efficiency. Shorter ex vivo transduction times in conjunction with the reduction of oxidative stress have been demonstrated to improve the efficacy of gene transduction in FA HSCs and may be promising for advancing FA gene therapy[84].

Last but not least, the integration of the therapeutic vector close to a proto-oncogene and the subsequent growth of a malignant clone constitute the ongoing risk of leukemia associated with gene therapy. The effectiveness and safety of gene therapy for FA may be further enhanced by advancements in conditioning protocols and the creation of self-inactivating retroviral and lentiviral vectors.

Endocrine dysfunction therapy. For many FA patients, hypothyroidism is noted. Thyroid treatment for seven months significantly improved the growth of FA children with short height, according to one study, indicating that thyroid treatment may be beneficial for these kids[85].

Growth hormone shortage affects between 50% and 70% of FA children, and additional growth hormone is typically administered to these individuals[86].

Long-term growth hormone therapy may or may not raise the risk of AML or other cancers; this is still debatable.

Treatment of cancer. AML and SCCs of the head, neck, and gynecological system are highly prevalent in FA patients[87].Treatment and management of FA-related malignancies remain a significant problem due to the extended survival following successful transplantation. Treatment of cancer connected to FA must be different from that of non-FA patients due to the cytotoxicity of chemo- and radiotherapeutic regimens for FA patients. Clinical care of FA patients must prioritize cancer prevention and vigilant cancer surveillance. To rule out premalignant clonal expansion, FA patients need yearly bone marrow aspirates. They also need regular dental exams to rule out early oral cavity SCCs. All FA patients should have HPV vaccinations, and women with FA need regular gynecologic checks to detect early SCCs. There are certain cancer patterns unique to the FA subtype. For example, individuals belonging to subtype D1 exhibit an earlier onset and a higher frequency of solid tumors and leukemia. Wilms tumor, neuroblastoma, and brain tumors like medulloblastoma are among the many tumors that are related to FANCD1 mutations [88][89].Furthermore, heterozygote carriers from the J, O, N, and D1 families of FA subtype D1 may be more susceptible to pancreatic, ovarian, and breast malignancies.

X. COMPLICATIONS

The four main complications of Fanconi anemia include acute myeloid leukemia, myelodysplastic syndrome (MDS), aplastic anemia, and specific solid malignancies [90].

Like how the abnormal FA gene is linked to several cancers, Fanconi anemia is linked to several tumors[91]. Cancer cells are hypersensitive to chemotherapeutic medicines, viruses, and radiation due to defects in genes of the Fanconi anemia pathway, which are essential for DNA repair and cell cycle checkpoints. Cells proliferate uncontrollably when the DNA repair machinery is compromised and cell cycle checkpoints are unstable. Squamous cell carcinomas of the head, neck, and upper esophagus as well as carcinomas of the vulva, anus, and cervix are common forms of cancer that have a 50-fold increased risk when compared to cases where Fanconi anemia connection is absent. The most prevalent discovery is myelodysplastic syndrome, which has a chance that is 6000 times higher than that of the normal population. The second most frequent malignancy, acute myelogenous leukemia, has a 700-fold increased risk in comparison to the general population. It has been shown that clonal mosaicism in Fanconi anemia causes aging and malignancies[92].

Furthermore, Fanconi anemia registries show that by the time they are 40 years old, 90% of patients have bone marrow failure[93]. Pancytopenia is eventually caused by bone marrow failure[94]. Numerous endocrine diseases are either related to androgen therapy and/or HCT, or they are intrinsic to molecular abnormalities. Short stature from growth hormone deficiency, hypothyroidism (found in about 60% of patients), adrenal dysfunction from exogenous ACTH, and pancreatic islet dysfunction linked to glucose intolerance, dyslipidemia, and infertility from

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

hypogonadism are all possible outcomes of structural disruption of the hypothalamus-pituitary axis. Peliosis hepatis and benign and malignant liver tumors are brought on by androgen therapy[95].

XI. PREVENTION AND PATIENT EDUCATION

Given that Fanconi anemia is inherited in a hereditary manner and that the patient is typically a kid when the disease first manifests, family members must be informed about and comprehend the severity of the condition. To improve patient compliance and the patient-clinician interaction, genetic counseling for the condition aids in providing family members with adequate patient education. When a kid has Fanconi anemia, other family members—especially siblings—need to be tested for the disease as well, either to detect the condition early or to avoid future births with genetic problems[96]. Recent research has demonstrated that while the biallelic patient has an increased risk of developing cancer, their heterozygote relatives do not experience the same drawback[97].This is not always the case; marriages within communities or cultures do not ensure this.

To assess whether the siblings could receive a hematopoietic stem cell transplant, a chromosomal breakage test, and HLA matching are required. Parents should get education that includes information on the indications and symptoms of the condition, the treatment strategy, and the disease process. All interventions should be explained to parents, along with any health risks and the advantages of one over the other. Patients can select the most appropriate course of treatment following in-depth discussion.

XII. CONCLUSION

A rare genetic condition called Fanconi anemia affects the bone marrow and is characterized by poor DNA repair. Physicians need to be aware of physical deformities, pancytopenia, and a higher chance of cancer. Genetic testing is a part of diagnosis. Hematopoietic stem cell transplantation, supportive care, and problem monitoring are all part of management. Because Fanconi anemia is hereditary, genetic counseling is essential. Because FA has numerous unique characteristics, research and testing on FA may help us understand the mechanisms underlying FA and other human genetic illnesses, aging, and cancer, as well as potential treatment options. In 1988, a patient with FA underwent the first successful use of human cord blood transplantation; the patient is currently alive and well.

It can be difficult to diagnose FA patients, especially in the condition's early stages. Given that Fanconi anemia disease (FA) is a genetically and phenotypically heterogeneous disease and has many clinical symptoms with numerous group diseases/syndromes, mismanagement resulting from misdiagnosis of FA has been reported in several locations and nations. Because the majority of FA proteins in the core complex lack an enzymatic motif, which makes it difficult to understand their molecular functions, research has not yet been able to pinpoint the precise biological activities and roles of the FA proteins.

A timely diagnosis is critical for any hereditary illness. Genetic counseling is crucial in both educating the patient's family members about the disease's progression and preventing it from striking the patient's offspring. The fact that prompt diagnosis and genetic counseling are necessary to begin the patient's therapy as soon as feasible must be thoroughly understood by the doctor. The availability of prenatal and preimplantation genetic diagnoses should be discussed with the child's parents. This will contribute to lessening the impact of hereditary illnesses on society.

In this review, we provide an overview of Fanconi anemia a rare disease incidence, genetics, pathophysiology, identification of FA genes and delineation of FA pathways, symptoms and indications, diagnosis, management and complications. The article also reviewed the prevention of FA by improving patient education.

ACKNOWLEDGEMENT

We appreciate the invaluable assistance provided by our Principal, the Head of the Department of Pharmacy Practice, Associate professor and the JKKMMRF's Annai JKK Sampoorani Ammal College of Pharmacy.

REFERENCES

[1]. Chandrasekharappa SC, Lach FP, Kimble DC, Kamat A, Teer JK, Donovan FX, Flynn E, Sen SK, Thongthip S, Sanborn E, Smogorzewska A, Auerbach AD, Ostrander EA., NISC Comparative Sequencing Program. Massively parallel sequencing, aCGH, and RNA-Seq technologies provide a comprehensive molecular diagnosis of Fanconi anemia. Blood. 2013 May 30;121(22):e138-48. [PMC free article] [PubMed] [Reference list]
[2]. Auerbach A D.Fanconi anemia and its diagnosis *Mutat Res* 2009668(1-2):4–10. [PMC free article] [PubMed] [Google Scholar] [Ref list]
[3]. Fanconi G. Familiäre infantile perniziosaartige Anämie (pernizioses Blutbild und Konstitution). Jahrb Kinderh 1927;117:257-80.
[4]. Schmid W, Scharer K, Baumann T, et al. Chromosomal fragility in familial panmyelopathy (Fanconi type). Schweiz Med Wochenschr 1965;95:1461-4. [PubMed]
[5]. Fanconi G. Familial constitutional panmyelocytopathy, Fanconi's anemia (F.A.). I. Clinical aspects. Semin Hematol 1967;4:233-40. [PubMed]
[6]. Moldovan GL, D'Andrea AD. How the fanconi anemia pathway guards the genome. Annu Rev Genet. 2009;43:223-49. [PMC free article] [PubMed] [Reference list]
[7]. Green AM, Kupfer GM. Fanconi anemia. Hematol Oncol Clin North Am. 2009 Apr;23(2):193-214. [PMC free article] [PubMed] [Reference list].
[8]. Bagby GC, Alter BP. Fanconi anemia. Semin Hematol. 2006 Jul;43(3):147-56. [PubMed] [Reference list]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

[9]. de Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia, Mutat Res, 2009, vol. 668 1-2(pg. 11-19).
[10]. Kutler DI, Singh B, Satagopan J, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR), Blood, 2003, vol. 101 4(pg. 1249-1256) .
[11]. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia, Blood, 2003, vol. 101 3(pg. 822-826)
[12]. Dufour C, Pierri F. Modern management of Fanconi anemia. Hematology Am Soc Hematol Educ Program. 2022 Dec 09;2022(1):649-657. [PMC free article] [PubMed] [Reference list]
[13]. Mehta PA, Davies SM, Leemhuis T, Myers K, Kernan NA, Prockop SE, Scaradavou A, O'Reilly RJ, Williams DA, Lehmann L, et al: Radiation-free, alternative-donor HCT for Fanconi anemia patients: Results from a prospective multi-institutional study. Blood. 129:2308–2315. 2017.PubMed/NCBI View Article : Google Scholar
[14]. Ebens CL, MacMillan ML and Wagner JE: Hematopoietic cell transplantation in Fanconi anemia: Current evidence, challenges and recommendations. Expert Rev Hematol. 10:81–97. 2017.PubMed/NCBI View Article : Google Scholar.
[15]. Moustacci E. Fanconi anemia. Orphanet 2002;1-5.
[16]. Auerbach AD, Rogatko A, Schroeder-Kurth TM. International Fanconi Anemia Registry: relation of clinical symptoms to diepoxybutane sensitivity. Blood 1989;73:391-6. [PubMed]
[17]. Tipping AJ, Pearson T, Morgan NV, et al. Molecular and genealogical evidence for a founder effect in Fanconi anemia families of the Afrikaner population of South Africa. Proc Natl Acad Sci U S A 2001;98:5734-9. [PubMed]
[18]. Tischkowitz MD, Hodgson SV. Fanconi anaemia. J Med Genet 2003;40:1-10. [PubMed]
[19]. Tipping AJ, Pearson T, Morgan NV, et al. Molecular and genealogical evidence for a founder effect in Fanconi anemia families of the Afrikaner population of South Africa. Proc Natl Acad Sci U S A 2001;98:5734-9. [PubMed]
[20]. Rosenberg PS, Tamary H, Alter BP. How high are carrier frequencies of rare recessive syndromes? Contemporary estimates for Fanconi Anemia in the United States and Israel. Am J Med Genet A 2011;155A:1877-83. [PubMed]
[21]. Meetei A R, Levitus M, Xue Y. X-linked inheritance of Fanconi anemia complementation group B. *Nat Genet.* 2004;36(11):1219–1224. [PubMed] [Google Scholar] [Ref list]
[22]. Wang A T, Kim T, Wagner J E. A dominant mutation in human RAD51 reveals its function in DNA interstrand crosslink repair independent of homologous recombination. *Mol Cell.* 2015;59(03):478–490. [PMC free article] [PubMed] [Google Scholar] [Ref list].
[23]. Bagby G. Recent advances in understanding hematopoiesis in Fanconi anemia. *F1000 Res.* 2018;7:105. [PMC free article] [PubMed] [Google Scholar] [Ref list]
[24]. NISC Comparative Sequencing Program . Chandrasekharappa S C, Lach F P, Kimble D C. Massively parallel sequencing, aCGH, and RNA-Seq technologies provide a comprehensive molecular diagnosis of Fanconi anemia. *Blood.* 2013;121(22):e138–e148. [PMC free article] [PubMed] [Google Scholar] [Ref list]
[25]. Kee Y, D'Andrea A D. Expanded roles of the Fanconi anemia pathway in preserving genomic stability. *Genes Dev.* 2010;24(16):1680–1694. [PMC free article] [PubMed] [Google Scholar] [Ref list]
[26]. George M, Solanki A, Chavan N. A comprehensive molecular study identified 12 complementation groups with 56 novel FANC gene variants in Indian Fanconi anemia subjects. *Hum Mutat.* 2021;42(12):1648–1665. [PubMed] [Google Scholar] [Ref list]
[27]. Adachi D, Oda T, Yagasaki H. Heterogeneous activation of the Fanconi anemia pathway by patient-derived FANCA mutants. *Hum Mol Genet.* 2002;11(25):3125–3134. [PubMed] [Google Scholar] [Ref list]
[28]. D'Andrea AD. Susceptibility pathways in Fanconi's anemia and breast cancer. *N Engl J Med.* 2010;362(20):1909–1919.**View this article via: PubMed CrossRef Google Scholar**.
[29]. Olson TS. Management of Fanconi anemia beyond childhood. Hematology Am Soc Hematol Educ Program. 2023 Dec 08;2023(1):556-562. [PMC free article] [PubMed] [Reference list].
[30]. Altintas B, Giri N, McReynolds LJ, Best A, Alter BP. Genotype-phenotype and outcome associations in patients with Fanconi anemia: the National Cancer Institute cohort. Haematologica. 2023 Jan 01;108(1):69-82. [PMC free article] [PubMed] [Reference list]
[31]. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006 Jun 01;107(11):4223-33. [PubMed] [Reference list]
[32]. Kennedy RD, Chen CC, Stuckert P, Archila EM, De la Vega MA, Moreau LA, Shimamura A, D'Andrea AD. Fanconi anemia pathway-deficient tumor cells are hypersensitive to inhibition of ataxia telangiectasia mutated. J Clin Invest. 2007 May;117(5):1440-9. [PMC free article] [PubMed] [Reference list]
[33]. D'Andrea AD, Grompe M. The Fanconi anemia/BRCA pathway. Nat Rev Cancer. 2003 Jan;3(1):23-34. [PubMed] [Reference list].
[34]. Longerich S, Li J, Xiong Y, Sung P, Kupfer GM. Stress and DNA repair biology of the Fanconi anemia pathway. Blood. 2014 Oct 30;124(18):2812-9. [PMC free article] [PubMed] [Reference list].
[35]. Giampietro PF, Adler-Brecher B, Verlander PC, Pavlakis SG, Davis JG, Auerbach AD. The need for more accurate and timely diagnosis in Fanconi anemia: a report from the International Fanconi Anemia Registry. Pediatrics. 1993;91(6):1116–1120.
[36]. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. J Clin Endocrinol Metab. 2007;92(7):2624–2631.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

[37]. Elder DA, et al. Abnormalities in glucose tolerance are common in children with fanconi anemia and associated with impaired insulin secretion. Pediatr Blood Cancer. 2008;51(2):256–260.
[38]. Wajnrajch MP, et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. Pediatrics. 2001;107(4):744–754.
[39]. Rietschel P, et al. Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. J Clin Endocrinol Metab. 2001;86(2):504–510.
[40]. Butturini A, Gale RP, Verlander PC, Adler-Brecher B, Gillio AP, Auerbach AD. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. Blood. 1994;84(5):1650–1655.
[41]. Kutler DI, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood. 2003;101(4):1249–1256.
[42]. Meyer S, et al. Fanconi anemia (FA)-associated 3q gains in leukemic transformation consistently target EVI1, but do not affect low TERC expression in FA. Blood. 2011;117(22):6047–6050.
[43]. Meyer S, et al. Amplification and translocation of 3q26 with overexpression of EVI1 in Fanconi anemia-derived childhood acute myeloid leukemia with biallelic FANCD1/BRCA2 disruption. Genes Chromosomes Cancer. 2007;46(4):359–372.
[44]. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006;107(11):4223–4233.
[45]. Kutler DI, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg. 2003;129(1):106–112.
[46]. Alter BP, et al. Fanconi's anaemia and pregnancy. Br J Haematol. 1991;77(3):410–418.View this article via: PubMed CrossRef Google Scholar.
[47]. Parmar K, D'Andrea A, Niedernhofer LJ. Mouse models of Fanconi anemia. Mutat Res. 2009;668(1–2):133–140.
[48]. Koomen M, et al. Reduced fertility and hypersensitivity to mitomycin C characterize Fancg/Xrcc9 null mice. Hum Mol Genet. 2002;11(3):273–281
[49]. Sy SM, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci U S A 2009;106:7155-60.
[50]. [PubMed]---Oostra AB, Nieuwint AW, Joenje H, et al. Diagnosis of fanconi anemia: chromosomal breakage analysis. Anemia 2012;2012:238731.
[51]. Meetei AR, Levitus M, Xue Y, et al. X-linked inheritance of Fanconi anemia complementation group B. Nat Genet 2004;36:1219-24. [PubMed].
[52]. Castella M, Pujol R, Callén E, et al. Chromosome fragility in patients with Fanconi anaemia: diagnostic implications and clinical impact. J Med Genet 2011;48:242-50.
[53]. Faivre L, Guardiola P, Lewis C, et al. Association of complementation group and mutation type with clinical outcome in Fanconi anemia. European Fanconi Anemia Research Group. Blood 2000;96:4064-70.
[54]. Futaki M, Yamashita T, Yagasaki H, et al. The IVS4 + 4 A to T mutation of the Fanconi anemia gene FANCC is not associated with a severe phenotype in Japanese patients. Blood 2000;95:1493-8. [PubMed]
[55]. Hodson C, Walden H. Towards a molecular understanding of the fanconi anemia core complex. Anemia 2012;2012:926787.
[56]. Ogilvie P, Hofmann U B, Bröcker E B, Hamm H. [Skin manifestations of Fanconi anemia] *Hautarzt.* 2002;53(04):253–257. [PubMed] [Google Scholar] [Ref list]
[57]. Yamashita T, Nakahata T. Current knowledge on the pathophysiology of Fanconi anemia: from genes to phenotypes. *Int J Hematol.* 2001;74(01):33–41. [PubMed] [Google Scholar] [Ref list]
[58]. Alter B P. Fanconi's anemia and malignancies. *Am J Hematol.* 1996;53(02):99–110. [PubMed] [Google Scholar] [Ref list]
[59]. [59] Young N S, Alter B P.Clinical features of Fanconi's anemia Philadelphia, PA: Saunders; 1994275–309.. 20 [Google Scholar] [Ref list],
[60]. European Fanconi Anemia Research Group . Faivre L, Guardiola P, Lewis C. Association of complementation group and mutation type with clinical outcome in Fanconi anemia. *Blood.* 2000;96(13):4064–4070. [PubMed] [Google Scholar] [Ref list]
[61]. Wajnrajch M P, Gertner J M, Huma Z. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. *Pediatrics.* 2001;107(04):744–754. [PubMed] [Google Scholar] [Ref list],
[62]. Hou J W, Wang T R. Differentiation of Fanconi anemia from aplastic anemia by chromosomal breakage test. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.* 1997;38(02):121–126. [PubMed] [Google Scholar] [Ref list]
[63]. Auerbach A D.Fanconi anemia and its diagnosis *Mutat Res* 2009668(1-2):4–10. [PMC free article] [PubMed] [Google Scholar] [Ref list]
[64]. Yamashita T, Wu N, Kupfer G, et al. Clinical variability of Fanconi anemia (type C) results from expression of an amino terminal truncated Fanconi anemia complementation group C polypeptide with partial activity. Blood 1996;87:4424-32. [PubMed]
[65]. Cervenka J, Arthur D, Yasis C. Mitomycin C test for diagnostic differentiation of idiopathic aplastic anemia and Fanconi anemia. Pediatrics 1981;67:119-27. [PubMed]
[66]. Auerbach AD. Fanconi anemia diagnosis and the diepoxybutane (DEB) test. Exp Hematol 1993;21:731-3. [PubMed]
[67]. Pulsipher M, Kupfer GM, Naf D, et al. Subtyping analysis of Fanconi anemia by immunoblotting and retroviral gene transfer. Mol Med 1998;4:468-79. [PubMed]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

[68]. Schindler D and H. Hoehn H. eds. Flow cytometric testing for syndromes with chromosomal instability, aplastic anemia and related hematological disorders in Diagnostic Cytogenetics. Heidelberg, Germany: Springer, 1999:269-81.
[69]. Chandra S, Levran O, Jurickova I, et al. A rapid method for retrovirus-mediated identification of complementation groups in Fanconi anemia patients. Mol Ther 2005;12:976-84. [PubMed]
[70]. Guidelines for Diagnosis and Management, Fanconi Anemia, Third Edition, 2008;P38-9
[71]. Ameziane N, Sie D, Dentro S, et al. Diagnosis of fanconi anemia: mutation analysis by next-generation sequencing. Anemia 2012;2012:132856.
[72]. Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. Hematology Am Soc Hematol Educ Program. 2007;2007:29–39.
[73]. Scheckenbach K, et al. Treatment of the bone marrow failure in Fanconi anemia patients with danazol. Blood Cells Mol Dis. 2012;48(2):128–131.
[74]. Alter BP, Caruso JP, Drachtman RA, Uchida T, Velagaleti GV, Elghetany MT. Fanconi anemia: myelodysplasia as a predictor of outcome. Cancer Genet Cytogenet. 2000;117(2):125–131.
[75]. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. Am J Hematol. 2004;77(3):257–267
[76]. MacMillan ML, Wagner JE. Haematopoeitic cell transplantation for Fanconi anaemia — when and how? Br J Haematol. 2010;149(1):14–21.
[77]. Zanis-Neto J, et al. Low-dose cyclophosphamide conditioning for haematopoietic cell transplantation from HLA-matched related donors in patients with Fanconi anaemia. Br J Haematol. 2005;130(1):99–106.
[78]. Pasquini R, et al. HLA-matched sibling hematopoietic stem cell transplantation for fanconi anemia: comparison of irradiation and nonirradiation containing conditioning regimens. Biol Blood Marrow Transplant. 2008;14(10):1141–1147.
[79]. Shimada A, et al. Excellent outcome of allogeneic bone marrow transplantation for Fanconi anemia using fludarabine-based reduced-intensity conditioning regimen. Int J Hematol. 2012;95(6):675–679.
[80]. MacMillan ML, et al. Haematopoietic cell transplantation in patients with Fanconi anaemia using alternate donors: results of a total body irradiation dose escalation trial. Br J Haematol. 2000;109(1):121–129.
[81]. Verlinsky Y, Rechitsky S, Schoolcraft W, Strom C, Kuliev A. Preimplantation diagnosis for Fanconi anemia combined with HLA matching. JAMA. 2001;285(24):3130–3133.
[82]. Gluckman E, et al. Bone marrow transplantation for Fanconi anemia. Blood. 1995;86(7):2856–2862.
[83]. Watts KL, Delaney C, Humphries RK, Bernstein ID, Kiem HP. Combination of HOXB4 and Delta-1 ligand improves expansion of cord blood cells. Blood. 2010;116(26):5859–5866.
[84]. Becker PS, et al. Preclinical correction of human Fanconi anemia complementation group A bone marrow cells using a safety-modified lentiviral vector. Gene Ther. 2010;17(10):1244–1252.
[85]. Eyal O, Blum S, Mueller R, Smith FO, Rose SR. Improved growth velocity during thyroid hormone therapy in children with Fanconi anemia and borderline thyroid function. Pediatr Blood Cancer. 2008;51(5):652–656.
[86]. Dupuis-Girod S, Gluckman E, Souberbielle JC, Brauner R. Growth hormone deficiency caused by pituitary stalk interruption in Fanconi's anemia. J Pediatr. 2001;138(1):129–133.
[87]. Alter BP, Greene MH, Velazquez I, Rosenberg PS. Cancer in Fanconi anemia. *Blood.* 2003;101(5):2072.
[88]. Frappart PO, Lee Y, Lamont J, McKinnon PJ. BRCA2 is required for neurogenesis and suppression of medulloblastoma. *EMBO J.* 2007;26(11):2732–2742.
[89]. Hirsch B, et al. Association of biallelic BRCA2/FANCD1 mutations with spontaneous chromosomal instability and solid tumors of childhood. *Blood.* 2004;103(7):2554–2559.
[90]. Alter BP. Fanconi anemia and the development of leukemia. Best Pract Res Clin Haematol. 2014 Sep-Dec;27(3-4):214-21. [PMC free article] [PubMed] [Reference list]
[91]. Nepal M, Che R, Zhang J, Ma C, Fei P. Fanconi Anemia Signaling and Cancer. Trends Cancer. 2017 Dec;3(12):840-856. [PMC free article] [PubMed] [Reference list]
[92]. Reina-Castillón J, Pujol R, López-Sánchez M, Rodríguez-Santiago B, Aza-Carmona M, González JR, Casado JA, Bueren JA, Sevilla J, Badel I, Català A, Beléndez C, Dasí MÁ, Díaz de Heredia C, Soulier J, Schindler D, Pérez-Jurado LA, Surrallés J. Detectable clonal mosaicism in blood as a biomarker of cancer risk in Fanconi anemia. Blood Adv. 2017 Jan 24;1(5):319-329. [PMC free article] [PubMed] [Reference list].
[93]. Kutler DI, Singh B, Satagopan J, Batish SD, Berwick M, Giampietro PF, Hanenberg H, Auerbach AD. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood. 2003 Feb 15;101(4):1249-56. [PubMed] [Reference list]
[94]. Kelaidi C, Makis A, Petrikkos L, Antoniadi K, Selenti N, Tzotzola V, Ioannidou ED, Tsitsikas K, Kitra V, Kalpini-Mavrou A, Fryssira H, Polychronopoulou S. Bone Marrow Failure in Fanconi Anemia: Clinical and Genetic Spectrum in a Cohort of 20 Pediatric Patients. J Pediatr Hematol Oncol. 2019 Nov;41(8):612-617. [PubMed] [Reference list]
[95]. Rose SR, Myers KC, Rutter MM, Mueller R, Khoury JC, Mehta PA, Harris RE, Davies SM. Endocrine phenotype of children and adults with Fanconi anemia. Pediatr Blood Cancer. 2012 Oct;59(4):690-6. [PubMed] [Reference list]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP081

[96]. Repczynska A, Julga K, Skalska-Sadowska J, Kacprzak MM, Bartoszewska-Kubiak A, Lazarczyk E, Loska D, Drozniewska M, Czerska K, Wachowiak J, Haus O. Next-generation sequencing reveals novel variants and large deletion in FANCA gene in Polish family with Fanconi anemia. Orphanet J Rare Dis. 2022 Jul 19;17(1):282. [PMC free article] [PubMed] [Reference list]

[97]. McReynolds LJ, Giri N, Leathwood L, Risch MO, Carr AG, Alter BP. Risk of cancer in heterozygous relatives of patients with Fanconi anemia. Genet Med. 2022 Jan;24(1):245-250. [PubMed] [Reference list]