



## REVIEW ARTICLE

# Fanconi anemia and risk of diverse types of cancer: An overview

Bintoo Sharma, Ranjeet Kumar, Harsh Tyagi, Nikita Khera, Megha Bajaj

Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India

### ABSTRACT

Fanconi anemia (FA) is a rare genetic disorder caused by a mistake in DNA repair that results in a variety of clinical signs and symptoms with varied incidence, most notably progressive bone marrow loss (depending on the affected gene), congenital abnormalities, and a propensity for malignancy. Cancer-prone FA is an unusual condition caused by alterations in at least 22 genes. DNA repair, in particular interstrand DNA crosslink (ICL) repair, is associated with the FA pathway. Cellular susceptibility to DNA cross-linking substances like diepoxybutane is a feature of FA. The report was mailed to 34 Fanconi Canada participants in August 2000 who also had FA confirmed by chromosomal breakage. FA is more prevalent among Spanish Gypsies, Afrikaners, and Ashkenazi Jews in addition to being more prevalent among Ashkenazi Jews. The bone marrow failure of FA can be effectively treated with androgens and hematological growth factors, but the majority of patients develop resistance to these medications. Hematopoietic stem cell transplantation is an option for these patients if a donor is available.

**KEY WORDS:** Ataxia telangiectasia mutated related, Bone marrow transplantation, Bone marrow failure, Diepoxybutane, FA-BRCA pathway, Fanconi anemia, Implantation genetic diagnosis, Monoubiquitination

### INTRODUCTION

Dr. Guido Fanconi first identified Fanconi anemia (FA) in a family of three siblings with several physical abnormalities and pernicious anemia in 1927.<sup>[1]</sup> FA is a rare genetic disorder caused by a mistake in DNA repair that results in a variety of clinical signs and symptoms with varied incidence, most notably progressive bone marrow loss (depending on the affected gene), congenital abnormalities, and a propensity for malignancy as shown in Figure 1.<sup>[2]</sup> An autosomal recessive disorder called FA is linked to congenital malformations, increasing pancytopenia, and a propensity for malignancy.<sup>[3]</sup> Guido Fanconi encountered a family whose three brothers expired from a condition similar to pernicious anemia with a variety of congenital defects but without symptoms of generally enhanced hemolysis during his pediatric residency at the Children's Hospital of the University of Zurich. Several further case reports have led to increased inquiry over the etiology and genetic pattern of this disease. Researchers

found that cells from FA patients exhibited a higher rate of chromosomal errors than those from healthy controls, nearly 40 years after Fanconi first described the condition.<sup>[4]</sup> When bone marrow failure (BMF) manifests at a median age of 7 years, it is diagnosed.<sup>[5]</sup> Cancer-prone FA is an unusual condition caused by alterations in at least 22 genes.<sup>[6]</sup> DNA repair, in particular interstrand DNA crosslink (ICL) repair, is associated with the FA pathway. Cellular susceptibility to DNA cross-linking substances like diepoxybutane (DEB) is a feature of FA.<sup>[7]</sup> The traditional clinical profile of FA includes café au lait patches, small stature, anomalies of the thumb and radial rays, and microcephaly. The majority of cases of progressive BMF are seen between the ages of 10 and 20. However, affected individuals might also present with a severe phenotype requiring complex procedures

#### Address for Correspondence:

Ranjeet Kumar

E-mail: ranjeetkumar2784@gmail.com

#### Access this article online

**Website:**

<http://isfcppharmaspire.com>

**DOI:**

10.56933/Pharmaspire.2023.15106

**Date of Submission:** 11 April 2023

**Date of Revision:** 25 April 2023

**Date of Acceptance:** 27 April 2023

for various congenital abnormalities and malignant sequelae early in life, or with a more modest phenotype and hematological and neoplastic issues in their third and fourth decades.<sup>[8-11]</sup> At least 22 FA genes, FANCA-FANCW, can have hereditary pathogenic gene variations (PGVs) that induce FA; all but the X-linked FANCB are autosomal, and all but FANCR/RAD51 are acquired recessively.<sup>[11-14]</sup> The primary pattern of inheritance is autosomal recessive (genes FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG/XRCC9, FANCI, FANCI/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCP/ERCC4, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7, and FANCW/RFWD3).<sup>[13,15]</sup> FA is primarily caused by molecular defects in the homologous recombination DNA repair pathway, proteins, and other enzymes necessary for DNA repair after exposure to various alkylating agents, radiation, and cytotoxic drugs. The development of molecular genetic research has aided in the proper research of FA.<sup>[16]</sup> Each sector of science has benefited from research into the interactions between the FA and BRCA systems.

Although new uses for FA proteins are being discovered, they are believed to be involved in stress signaling, apoptosis in response to cell stress, and the production of inflammatory cytokines.<sup>[17]</sup> FA has been divided into 13 subgroups, each of which has been linked to alterations in a different gene.<sup>[18]</sup> According to their functions in FANCD2 monoubiquitination, FA proteins can be divided into three classes. Damage-induced monoubiquitination of FANCD2 and FANCI requires the FA core complex, which is made up of FANCA-C, E-G, L, and M.<sup>[19,20]</sup> In addition, it was discovered that several FA proteins were ATM/ATR barrier kinase downstream targets.<sup>[21]</sup> It has been demonstrated that ATR's phosphorylation of FANCI acts as a signal to activate the FA pathway.<sup>[22]</sup> In comparison to their phenotypic presentation, affected siblings with lower phenotypic traits were only identified after the diagnosis of FA in another impacted family member. In addition, patients with "Fanconi-like" bone marrow loss were previously thought to have Estren-Dameshek syndrome but had no congenital abnormalities.<sup>[23]</sup> Numerous examples of VACTERL with hydrocephalus and Baller-Gerold syndrome have been documented in the literature; however, when the patients had BMF and a successful chromosomal breakage test with a crosslinking agent, the diagnosis was revised to FA.<sup>[24]</sup>

## ETIOLOGY

The specific roles of the FA complex and the causes of cancers in FA are still unclear. To better understand genetic pathways and gene/environment interactions that influence the risks of certain malignancies in FA and the general population, it is important to identify patterns of cancer risk in FA. The report was mailed to 34 Fanconi Canada participants in August 2000 who also had FA confirmed by

chromosomal breakage. The risk is roughly 50 times more compared to the general population for all solid tumors, and many hundred to many thousand times greater compared to the general population for malignancies of the head-and-neck, esophagus, liver, vulva, and cervix.<sup>[25,26]</sup> Over 65% of cases of FA are caused by mutations in the FANCA gene, and the Fanconi Anaemia Mutation Database has identified more than 500 harmful variations of this gene.<sup>[27]</sup> Inherent susceptibility to DNA-damaging treatments including chemotherapy and radiation therapy.<sup>[28]</sup>

The FA/BRCA repair pathway, which identifies damage that covalently bonds the two DNA strands (interstrand crosslinking; ICL) and facilitates their repair through homologous monoubiquitination and recombination, uses all of the proteins encoded by the genes.<sup>[29]</sup> Exogenous substances, such as cancer chemotherapeutics, as well as endogenous agents, like alcohol metabolites, cigarette smoke, acetaldehyde, and malondialdehyde, cause ICLs to develop in DNA.<sup>[30]</sup>

## EPIDEMIOLOGY

Although FA is a rare hereditary causation of BMF with an incidence of about 1 in 130,000 births, it is also the most common.<sup>[31,32]</sup> In Israel, the carrier frequency is roughly 1:93, which is significantly higher than the anticipated 1:181 frequency in the United States.<sup>[5]</sup> FANCA, the gene most frequently altered in FA cases (60–70% of incidences), is preceded by FANCC (10–15%) and FANCG (10%).<sup>[33]</sup> FA is more prevalent among Spanish Gypsies, Afrikaners, and Ashkenazi Jews in addition to being more prevalent among Ashkenazi Jews.<sup>[5,34,35]</sup> FA directly impacts men, with a male-to-female ratio of 1.2:1. This is for unclear reasons.<sup>[17]</sup> FA patients run a high risk of developing serious hematologic illnesses such as acute myelogenous leukemia, aplastic anemia, myelodysplastic syndrome (MDS), and BMF without medication care.<sup>[36]</sup> Early attempts at SCT for FA (more than 20 years ago) were characterized by a high death rate, but more recent improvements in patient screening, HLA donor typing, and conditioned protocols have resulted in 5-year survival rates that are now as high as 70–94%.<sup>[37,38]</sup> Endocrine problems are present in many FA patients. Small height affects about 50% of FA people, which is correlated with hyperthyroidism and insufficient generation of growth hormones. Some FA people are of average height and do not appear to be producing enough growth hormone. FA is also connected to improper glucose or insulin metabolism.

FA patients typically have higher serum insulin levels than people with diabetes, who have decreased insulin. Around 8% of people with FA are said to have diabetes, and up to 72% of them have high insulin levels.<sup>[39,40]</sup> Even though in earlier studies the risk of pancytopenia was pegged at 84%, 20 years after the initial thrombocytopenia diagnosis.<sup>[41]</sup>

The details of 1301 FA patients' malignancies that were documented in the research between 1927 and 2001.<sup>[42]</sup> 220 (17%) of the 1301 patients had at least one cancer. The most common malignancy, leukemia, and especially AML, were found in 8.9% of patients, whereas solid tumors were found in 5.3% of patients. The majority (67%) of FA patients with solid tumors were female. Compared to the overall population, solid tumors developed at a younger age: 26 versus 68 years, respectively. All the FA patients who underwent bone marrow transplants (12/12) acquired mouth cancer, and they were all younger (21 and 28 years old, respectively) than the FA patients who had oral cancer but had not taken bone marrow transplantation (BMT).<sup>[43]</sup>

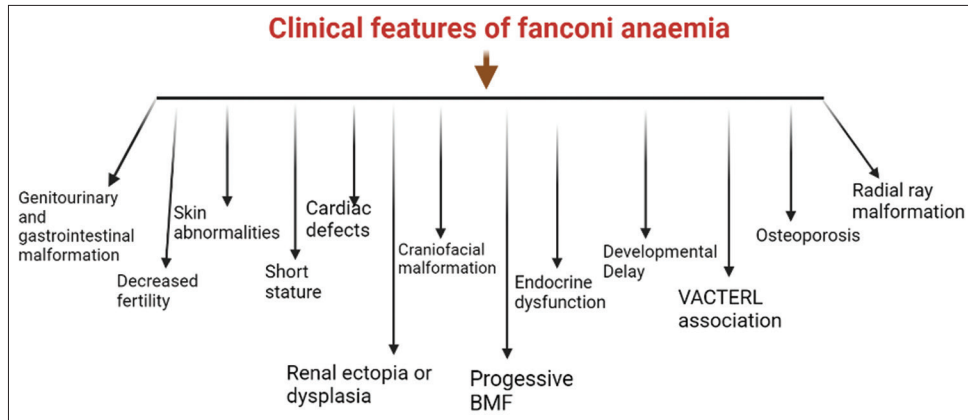
## INITIATION OF FA PATHWAY

The FA pathway, commonly known as the FA-BRCA pathway, is a critical system for DNA repair that recognizes DNA damage and coordinates responses to it, particularly for DNA inter stream crosslink (ICL) repair.<sup>[44]</sup> DNA damage can be divided into two primary groups: endogenous damage and exogenous damage. Most of the endogenous DNA damage is caused by chemically active DNA reacting with water and reactive oxygen species (ROS), which are both naturally occurring in cells, in hydrolytic and oxidative ways. Hereditary illnesses and sporadic cancers are fueled by these genetically predisposed interactions of DNA with chemicals from its immediate environment.<sup>[45]</sup> On the other side, exogenous DNA damage takes place when environmental, physical, and chemical factors harm the DNA. Alkylating agents, ionizing radiation, and crosslinking agents are a few examples. as shown in Figure 2.<sup>[46]</sup> The FA pathway is initiated by the histone-like MHF complex and the ATP-dependent DNA translocase FANCM (MHF1-MHF2-FAAP24), which detects the DNA damage region and attaches to it and attracts more FA protein.<sup>[47]</sup> ICLs harm both strands of the helix and are challenging to repair.<sup>[48]</sup> As a result, it appears that higher eukaryotes developed the FA pathway as a unique approach to handling this particular form of DNA damage. The primary role of the FA pathway appears to be the coordination of various repair activities from various classic repair pathways, such as homologous recombination (HR), translesion synthesis (TLS), and nucleotide excision repair (NER), to break down crosslinks.<sup>[49]</sup> The majority of FA patients have mutations in the genes that encode the core complex, with more than 60% having FANCA defects. As a result, it was among the first FA genes to be cloned. FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM are additional parts of the core complex. However, FAAP24 and FAAP100 mutations have not yet been linked to FA illness. Two more genes, FAAP24 and FAAP100, encode proteins that were discovered to be a component of the core complex and necessary for the activation of the FA pathway.<sup>[19,50]</sup> The key step in FA activation is thought to be monoubiquitination. Other parts, Outside of FANCD2-I

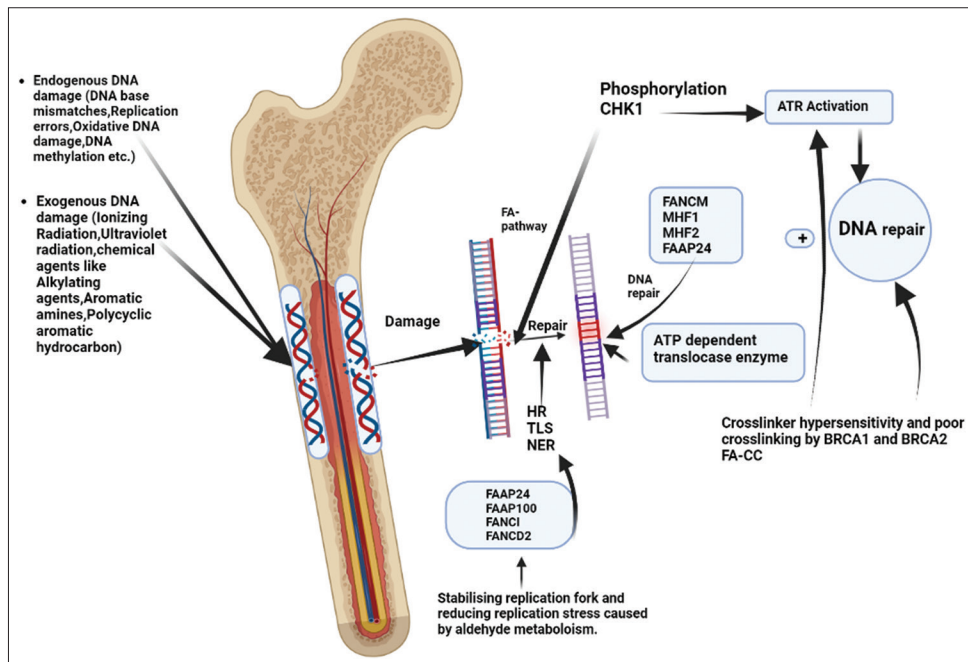
ubiquitination, of the core complex cannot be ignored. The phenotypes of FANCD2 knockdown can be improved by FANCD2 K561R-ubiquitin fusion. DT40 cells indicating that the location of the ubiquitin is irrelevant. Cells lacking the complement core complex.<sup>[51]</sup> While FANCI ubiquitination may improve repair, it is not necessary for the DNA repair process in the same way as FANCD2 ubiquitination is Estren and Dameshek.<sup>[22]</sup> Through its phosphorylation in response to ataxia telangiectasia and Rad3-related (ATR), FANCI offers a significant regulatory mechanism of the pathway. Independent of core complex activity, FANCI phosphorylation may be essential for its localization to chromatin.

This is supported by the finding that deletion of FANCI in DT40 cells eliminates FANCD2 ubiquitination, but this is restored when the cells are supplemented with a point mutation in the FANCI ubiquitination site, suggesting that aspects of FANCI other are essential for FA activation in addition to its ubiquitination site.<sup>[22]</sup> The second helicase in the FA pathway is FANCI, often referred to as BRIP1 or BACH1.<sup>[22]</sup> The S-phase checkpoint is masterly regulated by ATR, also known as Ataxia Telangiectasia Mutated Related.

ATR activation is dependent on the existence of (doi.org) RPA-coated single-stranded DNA (ssDNA) containing areas concerning certain classes of DNA replication stressors.<sup>[52]</sup> By phosphorylating CHK1, ATR synchronizes checkpoint activation with the conclusion of DNA repair. Crosslinker hypersensitivity and poor crosslinking are caused by defective ATR function. FANCD2 Radial genomic uncertainty brought on by massive monoubiquitination and buildup chromosomes.<sup>[21,53]</sup> The FA pathway is strongly associated with DNA repair at the cellular level. The FA genes encode proteins that play a key role in stabilizing replication forks and reducing replication stress, particularly that caused by cross-linker-induced and genotoxic stress brought on by aldehyde metabolism. The FA pathway is situated in the context of DNA repair at the cellular level. The FA genes encode proteins that play a key role in stabilizing replication forks and reducing replication stress, particularly that caused by cross-linker-induced and genotoxic stress brought on by aldehyde metabolism.<sup>[13,54,55]</sup> In the homologous recombination repair process of double-stranded DNA (ds-DNA) breaks, both BRCA1 and BRCA2 are crucial.<sup>[56,57]</sup> FA proteins I and D2 (ID) are monoubiquitinated by FA-CC in a crucial process that is regarded as a sign of FA integrity. CC's By activating proteins implicated in The FA route includes, such as FANCL, and promoting the effective ubiquitination of ID, the damage response kinases ATM and ATR also play a significant role in the FA cascade. A variety of endonucleases, including FANCO (RAD51C), which interacts with FANCP and resolves through the ICL, are recruited by the ubiquitinated ID complex. This unhooking process also causes breaks in the double-strand DNA, which must be repaired. BRCA2,



**Figure 1:** Clinical features in patients diagnosed with Fanconi anemia



**Figure 2:** Damage and repair of DNA in Fanconi anemia

FANCI, FANCD1 (PALB2), and FANCD2 proteins work along with other endonucleases to carry out this repair. The ID complex is de-ubiquitinated once the initial DNA damage has been repaired, and the entire apparatus (the FA-BRCA2 pathway) is subsequently turned off.<sup>[58]</sup> Despite addressing The FA route includes being a promising cancer therapy, there is still a long way to go until the laboratory discoveries are used in actual patient care.<sup>[58]</sup>

### TREATMENT WITH CO-RELATE TO DIAGNOSE

The BMF of FA can be effectively treated with androgens and hematological growth factors, but most patients develop resistance to these medications. Hematopoietic stem cell transplantation is an option for these patients if a donor is available. A novel method for detecting possible sibling donors for FA patients is called pre-implantation

genetic diagnosis (PGD).<sup>[59]</sup> The MMC or DEB chromosomal breakage test is the accepted method for diagnosing FA. This test should be carried out in labs with a lot of experience. The techniques include cultivating replicative (often PHA-stimulated) cells skin fibroblasts or peripheral blood T lymphocytes) in the modest dosages of either MMC or DEB present, preceded by the analysis of metaphase spreads for chromosomal radial chromosomes and breakage. On a negative test result despite the clinical environment being extremely suspect, in lymphocytes, it is important to evaluate skin fibroblasts since certain patients are mosaics where a single hematopoietic cell's molecular abnormality has been rectified by hematopoietic somatic mutations stem cell.<sup>[60,61]</sup> Lower amounts of conditioning medications are necessary to prevent fatal toxicities because non-FA patients are particularly sensitive to the chemotherapy and radiation that are often used to cure them.<sup>[62]</sup> Retrospective evidence shows that long-term



survivors still have a high chance of developing head and neck epithelial carcinoma despite such declines.<sup>[63]</sup> Due to a genetic defect repairing DNA, FA patients are highly radiosensitive.<sup>[64]</sup> Although FA is typically diagnosed before HNSCC manifests itself, the phenotypic variability of FA calls for a high index of suspicion in all adolescent or young adult patients who unpredictably develop HNSCC. Surprisingly, some FA patients show no overt medical symptoms of the illness.<sup>[17,65,66]</sup> Based on convincing findings in pertinent preclinical models, in 2018, the European Medicines Agency approved the use of gefitinib or afatinib as EGFR TKIs for FA-HNSCC.<sup>[67]</sup> Relative to the overall population, solid tumors developed at a younger age: 26 versus 68 years, respectively. Every FA patient undergoing a bone marrow transplant BMT was younger than the (BMT) and had mouth cancer on 12/12. Oral cancer patients with FA had not received BMT, 21 and 30 years old, respectively. This increased risk of solid tumors following prior BMT has been seen in additional research and is linked to complete body irradiation, high-intensity interval training, and chemotherapeutic dosage or prophylactic immunomodulatory therapy in favor of graft versus host disease.<sup>[43]</sup> A single genetic test cannot be utilized as a first step in the diagnosis of FA in unselected BMF patients because there are so many genes and mutations linked to the disease. The extraordinary sensitivity of FA cells to DNA ICL compounds like DEB or mitomycin C is the primary biological indicator of FA. For the diagnosis of FA, the chromosomal breakage test using these chemicals is the standard method.<sup>[17,68]</sup> The study of the cell cycle and evaluation of FANCD2 mono-ubiquitination are two additional blood tests that can positively identify patients with FA core.<sup>[69,70]</sup> The current standard of care for HNSCC when RT is used is intensity-modulated radiation (IMRT), which has superior locoregional control and a lower toxicity profile than previous three-dimensional conformal RT.<sup>[71]</sup> Cisplatin is the typical chemotherapeutic drug used for CRT. Cetuximab has been utilized in definite CRT, but less so now that several recent clinical trials have shown how inferior it is to cisplatin in HPV-positive HNSCC patients.<sup>[72]</sup> Some FA patients can successfully treat their bone marrow loss with androgen treatment. Hematopoietic abnormalities in patients with FA have been successfully treated with synthetic androgens like oxymetholone and danazol.<sup>[73,74]</sup> The current method of development involves swapping a defective gene with a normal gene. It is now possible to correct CD34+ in infected cells.<sup>[75]</sup> Pure red cell aplasia, or Diamond-Blackfan anemia, frequently manifests as abnormalities of the bone marrow.<sup>[76]</sup> In 88–100% of cases, Schwachman-diamond syndrome is primarily characterized by neutropenia.<sup>[77]</sup> Vaccination against the human papillomavirus (eur-lex.europa.eu) lowers the chance of gynecologic cancer in women and perhaps lowers the chance of oral cancer in everyone. In some people, granulocyte colony-stimulating factor (G-CSF) raises the neutrophil count. To maintain ANC above 1000/mm<sup>3</sup>, the G-CSF dose should be adjusted at the lowest dose and frequency conceivable.<sup>[78]</sup>

## FA ASSOCIATED WITH CANCER

Considering that people with FA are susceptible to several competing sources of morbidity and mortality is reflected in the absolute risk of cancer that has been seen in this population. A hematopoietic stem cell may develop into cancer when the bone marrow loss that is indicative of FA progresses and requires therapeutic BMT. A somatic cell may be cancerous, resulting in leukemia (often AML), or become cancerous and grow into a solid tumor. Therefore, we thought about struggling with death, BMT, AML, and the emergence of solid tumor hazards, in that the presence of (doi.org) even one of these circumstances could result in censorship. It modifies the other circumstances' natural histories. Considering the relationship, the relationship between leukemia and MDS is yet unclear developed in FA.<sup>[79]</sup> In addition to the extremely high incidence of AML patients with FA (actuarial risk of 52% for MDS and/or AML progression by age 40).<sup>[41]</sup> The breast/ovarian cancer risk protein BRCA2 is also among the FA proteins; it is referred to here as FANCD1/BRCA2.<sup>[80]</sup> The incidence of breast, ovarian, or pancreatic cancer is particularly high in heterozygote carriers of the BRCA2 mutation.<sup>[81-83]</sup> This discovery was made possible by several observations. First, those who carry the BRCA2 mutation heterozygously run a significant risk of developing breast, ovarian, or pancreatic cancer.<sup>[81,83]</sup> The most significant (doi.org) cancers that predispose FA patients to other cancers include gynecologic malignancies, head-and-neck cancers, liver tumors, and myeloid hematological malignancies.<sup>[13,84]</sup> It is well established that a defect in the mechanisms for DNA repair strongly correlates with certain forms of cancer: Imbalance and base deletion repair (MSH2/6 and MUTYH) for colorectal cancer; DNA damage response (DDR) genes (ATM) for leukemia; FA/HR pathway (BRCA1, BRCA2, and PALB2) for the breast, uterus, and prostate cancer; etc.<sup>[85,86]</sup> In dysplastic lesions of the head-and-neck, activator methylation was discovered to cause FANCC to become inactive at an initial stage.<sup>[87]</sup> The activator of FANCA and BRCA2 were repeatedly methylated in laryngeal squamous cell cancer.<sup>[88]</sup> In sporadic acute leukemia, the FANCC and FANCL activator were hypermethylated.<sup>[89]</sup>

## CONCLUSIONS

Fanconi anemia is a hereditary disease. Patients with FA have a higher risk of developing aplasia, MDS, and AML. A specialist multidisciplinary clinical and biochemical competence is required for FA patient follow-up. Understanding the sequential molecular and cellular mechanisms of the BMF and clonal evolution is crucial for effective treatment. Significant physical abnormalities put on by FA may have an impact on a person's growth and appearance. On the other hand, enhanced FA function brought on by gene copy number increase or transcriptional regulation is a trait that is common in a lot of cancers

and is frequently linked to innate or acquired resistance to chemotherapy that induces ICL. Ask your healthcare practitioner if you or your child has FA what to expect and how FA can influence your life.

### AUTHORS CONTRIBUTIONS

Mr. Bintoo Sharma is the major contributor to the writing, literature, and drafting of the manuscript; Mr. Ranjeet Kumar, Dr. Amit Sharma, Miss. Megha Bajaj, Miss. Nikita Khera, Mr. Harsh Tyagi is the major contributor in editing and drafting the manuscript, all authors read and approved the final manuscript.

### ACKNOWLEDGMENTS

We thank ISF College of Pharmacy, Moga, Punjab, for their constant support and guidance.

### CONFLICT OF INTEREST STATEMENT

The authors have declared that no competing interests exist.

### STATEMENT OF ETHICS

Not Applicable

### FUNDING SOURCES

There are no funding sources for this report.

### GUARANTOR OF THE MANUSCRIPT

Mr Ranjeet Kumar, the corresponding author of the manuscript.

### REFERENCES

- Wiedemann HR. Guido Fanconi (1892-1979) in memoriam. *Eur J Pediatr* 1979;32:131-2.
- Mamrak NE, Shimamura A, Howlett NG. Recent discoveries in the molecular pathogenesis of the inherited bone marrow failure syndrome Fanconi anemia. *Blood Rev* 2017;31:93-9.
- Alter BP. The bone marrow failure syndromes. In: *Hematology of Infancy and Childhood*. Philadelphia, PA: WB Saunders Co.; 1993. p. 216-316.
- Swift MR, Hirschhorn K. Fanconi's anemia: Inherited susceptibility to chromosome breakage in various tissues. *Ann Intern Med* 1966;65:496-503.
- 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 Part A* 2011;155:1877-83.
- Degan P, Cappelli E, Regis S, Ravera S. New insights and perspectives in Fanconi anemia research. *Trends Mol Med* 2019;25:167-70.
- Auerbach AD. Diagnosis of Fanconi anemia by diepoxybutane analysis. *Curr Protoc Hum Genet* 2003;37:8-7.
- Taylor AM, Rothblum-Oviatt C, Ellis NA, Hickson ID, Meyer S, Crawford TO, *et al.* Chromosome instability syndromes. *Nat Rev Dis Prim* 2019;5:1-20.
- Huck K, Hanenberg H, Gudowius S, Fenk R, Kalb R, Neveling K, *et al.* Delayed diagnosis and complications of Fanconi anemia at an advanced age-a paradigm. *Br J Haematol* 2006;133:188-97.
- Neveling K, Endt D, Hoehn H, Schindler D. Genotype-phenotype correlations in Fanconi anemia. *Mutat Res* 2009;668:73-91.
- Fiesco-Roa MO, Giri N, McReynolds LJ, Best AF, Alter BP. Genotype-phenotype associations in Fanconi anemia: A literature review. *Blood Rev* 2019;37:100589.
- Knies K, Inano S, Ramirez MJ, Ishiai M, Surrallés J, Takata M, *et al.* Biallelic mutations in the ubiquitin ligase RFW3 cause Fanconi anemia. *J Clin Invest* 2017;127:3013-27.
- Niraj J, Färkkilä A, D'Andrea AD. The Fanconi anemia pathway in cancer. *Annu Rev Cancer Biol* 2019;3:457-78.
- Wang AT, Kim T, Wagner JE, Conti BA, Lakh FP, Huang AL, *et al.* A dominant mutation in human RAD51 reveals its function in DNA interstrand crosslink repair independent of homologous recombination. *Mol Cell* 2015;59:478-90.
- Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anemia pathway: New players and new functions. *Nat Rev Mol Cell Biol* 2016;17:337-49.
- Bhandari J, Thada PK, Puckett Y. Fanconi anemia. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2022.
- Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev* 2010;24:101-22.
- Wang W. The emergence of a DNA-damage response network consisting of Fanconi anemia and BRCA proteins. *Nat Rev Genet* 2007;8:735-48.
- Ciccio A, Ling C, Coulthard R, Yan Z, Xue Y, Meetei AR, *et al.* Identification of FAAP24, a Fanconi anemia core complex protein that interacts with FANCM. *Mol Cell* 2007;25:331-43.
- Smogorzewska A, Matsuoka S, Vinciguerra P, McDonald 3<sup>rd</sup> ER, Hurov KE, Luo J, *et al.* Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. *Cell* 2007;129:289-301.
- Andreassen PR, D'Andrea AD, Taniguchi T. ATR couples FANCD2 monoubiquitination to the DNA damage response. *Genes Dev* 2004;18:1958-63.
- Ishiai M, Kitao H, Smogorzewska A, Tomida J, Kinomura A, Uchida E, *et al.* FANCI phosphorylation functions as a molecular switch to turn on the Fanconi anemia pathway. *Nat Struct Mol Biol* 2008;15:1138-46.
- Estren S, Dameshek W. Familial hypoplastic anemia of childhood: Report of eight cases in two families with the

- beneficial effect of splenectomy in one case. *Am J Dis Child* 1947;73:671-87.
24. Rossbach HC, Sutcliffe MJ, Haag MM, Grana NH, Rossi AR, Barbosa JL. Fanconi anemia in brothers initially diagnosed with VACTERL association with hydrocephalus, and subsequently with Baller-Gerold syndrome. *Am J Med Genet* 1996;61:65-7.
  25. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003;101:822-6.
  26. Socié G, Devergie A, Girinski T, Piel G, Ribaud P, Esperou H, *et al.* Transplantation for Fanconi's anemia: Long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *Br J Haematol* 1998;103:249-55.
  27. Dong H, Nebert DW, Bruford EA, Thompson DC, Joenje H, Vasilioiu V. Update of the human and mouse Fanconi anemia genes. *Hum Genomics* 2015;9:32.
  28. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. *Nat Rev Cancer* 2011;11:467-80.
  29. Nalepa G, Clapp DW. Fanconi anemia and cancer: An intricate relationship. *Nat Rev Cancer* 2018;18:168-85.
  30. Stone MP, Cho YJ, Huang H, Kim HY, Kozekov ID, Kozekova A, *et al.* Interstrand DNA cross-links induced by  $\alpha$ ,  $\beta$ -unsaturated aldehydes derived from lipid peroxidation and environmental sources. *Acc Chem Res* 2008;41:793-804.
  31. Dokal I, Vulliamy T. Inherited bone marrow failure syndromes. *Haematologica* 2010;95:1236.
  32. Aymun U, Iram S, Aftab I, Khaliq S, Ali N, Ahmed N, *et al.* Screening for mutations in two exons of FANCG gene in Pakistani population. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2017;161:158-63.
  33. Mehta PA, Tolar J. Fanconi Anemia. 2018. Available from: <https://www.mdpi.com/1999-4915/10/1/47> [Last accessed on 2022 Aug 30].
  34. Gille JJ, Floor K, Kerkhoven L, Ameziane N, Joenje H, de Winter JP. Diagnosis of Fanconi anemia: Mutation analysis by multiplex ligation-dependent probe amplification and PCR-based Sanger sequencing. *Anemia* 2012;2012:603253.
  35. Callén E, Casado JA, Tischkowitz MD, Bueren JA, Creus A, Marcos R, *et al.* A common founder mutation in FANCA underlies the world's highest prevalence of Fanconi anemia in Gypsy families from Spain. *Blood* 2005;105:1946-9.
  36. Kutler DI, Singh B, Satagopan J, Batish SD, Berwick M, Giampietro PF, *et al.* A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 2003;101:1249-56.
  37. Gluckman E, Auerbach AD, Horowitz MM, Sobocinski KA, Ash RC, Bortin MM, *et al.* Bone marrow transplantation for Fanconi anemia. *Blood* 1995;86:2856-62.
  38. Ebens CL, DeFor TE, Tryon R, Wagner JE, MacMillan ML. Comparable outcomes after HLA-matched sibling and alternative donor hematopoietic cell transplantation for children with Fanconi anemia and severe aplastic anemia. *Biol Blood Marrow Transplant* 2018;24:765-71.
  39. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. *J Clin Endocrinol Metab* 2007;92:2624-31.
  40. Elder DA, D'Alessio DA, Eyal O, Mueller R, Smith FO, *et al.* Abnormalities in glucose tolerance are common in children with Fanconi anemia and are associated with impaired insulin secretion. *Pediatr Blood Cancer* 2008;51:256-60.
  41. 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;84:1650-5.
  42. Alter BP. Cancer in Fanconi anemia, 1927-2001. *Cancer* 2003;97:425-40.
  43. Rosenberg PS, Socié G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005;105:67-73.
  44. Su X, Huang J. The Fanconi anemia pathway and DNA interstrand cross-link repair. *Protein Cell* 2011;2:704-11.
  45. Visconti R, Grieco D. New insights on oxidative stress in cancer. *Curr Opin Drug Discov Dev* 2009;12:240-5.
  46. Chatterjee N, Walker GC. Mechanisms of DNA damage, repair, and mutagenesis. *Environ Mol Mutagen* 2017;58:235-63.
  47. Collis SJ, Boulton SJ. FANCM: Fork pause, rewind, and play. *EMBO J* 2010;29:703-5.
  48. Schärer OD. DNA interstrand crosslinks: Natural and drug-induced DNA adducts that induce unique cellular responses. *ChemBiochem* 2005;6:27-32.
  49. Niedzwiedz W, Mosedale G, Johnson M, Ong CY, Pace P, Patel KJ. The Fanconi anemia gene FANCC promotes homologous recombination and error-prone DNA repair. *Mol Cell* 2004;15:607-20.
  50. Ling C, Ishii M, Ali AM, Medhurst AL, Neveling K, Kalb R, *et al.* FAAP100 is essential for the activation of the Fanconi anemia-associated DNA damage response pathway. *EMBO J* 2007;26:2104-14.
  51. Matsushita N, Kitao H, Ishiai M, Nagashima N, Hirano S, Okawa K, *et al.* A FancD2-monoubiquitin fusion reveals hidden functions of Fanconi anemia core complex in DNA repair. *Mol Cell* 2005;19:841-7.
  52. Ciccio A, Elledge SJ. The DNA damage response: Making it safe to play with knives. *Mol Cell* 2010;40:179-204.
  53. Pichierri P, Rosselli F. The DNA crosslink-induced S-phase checkpoint depends on ATR-CHK1 and ATR-NBS1-FANCD2 pathways. *EMBO J* 2004;23:1178-87.
  54. Langevin F, Crossan GP, Rosado IV, Arends MJ, Patel KJ. Fancd2 counteracts the toxic effects of naturally produced aldehydes in mice. *Nature* 2011;475:5358.
  55. Rosado IV, Langevin F, Crossan GP, Takata M, Patel KJ. Formaldehyde catabolism is essential in cells deficient for the Fanconi anemia DNA-repair pathway. *Nat Struct Mol Biol* 2011;18:1432-4.
  56. Chen CC, Feng W, Lim PX, Kass EM, Jasin M. Homology-directed repair and the role of BRCA1, BRCA2, and related proteins in genome integrity and cancer. *Annu Rev Cancer Biol* 2018;2:313-36.



57. Venkitaraman AR. Cancer suppression by the chromosome custodians, BRCA1 and BRCA2. *Science* 2014;343:1470-5.
58. Dan C, Pei H, Zhang B, Zheng X, Ran D, Du C. Fanconi anemia pathway and its relationship with cancer. *Genome Instab Dis* 2021;2:175-83.
59. Verlinsky Y, Rechitsky S, Schoolcraft W, Strom C, Kuliev A. Preimplantation diagnosis for Fanconi anemia combined with HLA matching. *JAMA* 2001;285:3130-3.
60. Mankad A, Taniguchi T, Cox B, Akkari Y, Rathbun RK, Lucas L, *et al.* Natural gene therapy in monozygotic twins with Fanconi anemia. *Blood* 2006;107:3084-90.
61. Gregory JJ Jr., Wagner JE, Verlander PC, Levran O, Batish SD, Eide CR, *et al.* Somatic mosaicism in Fanconi anemia: Evidence of genotypic reversion in lymphohematopoietic stem cells. *Proc Natl Acad Sci* 2001;98:2532-7.
62. Gluckman E. Radiosensitivity in Fanconi anemia: Application to the conditioning for bone marrow transplantation. *Radiother Oncol* 1990;18:88-93.
63. Alter BP. Fanconi's anemia, transplantation, and cancer. *Pediatr Transplant* 2005;9(Suppl 7):81-6.
64. Alter BP, Rosenberg PS. Natural history and management of Fanconi Anemia patients with head and neck cancer: A 10-year follow-up. *Laryngoscope* 2016;126:E229.
65. Giampietro PF, Verlander PC, Davis JG, Auerbach AD. Diagnosis of Fanconi anemia in patients without congenital malformations: An international Fanconi Anemia Registry Study. *Am J Med Genet* 1997;68:58-61.
66. Lach FP, Singh S, Rickman KA, Ruiz PD, Noonan RJ, Hymes KB, *et al.* Esophageal cancer as the initial presentation of Fanconi anemia in patients with a hypomorphic FANCA variant. *Cold Spring Harb Mol Case Stud* 2020;6:a005595.
67. Royce M, Osgood CL, Amatya AK, Fiero MH, Chang CG, Ricks TK, *et al.* FDA approval summary: Margetuximab plus chemotherapy for advanced or metastatic HER2-positive breast cancer. *Clin Cancer Res* 2022;28:1487-92.
68. Auerbach AD. Fanconi anemia and its diagnosis. *Mutat Res* 2009;668:4-10.
69. Seyschab H, Friedl R, Sun Y, Schindler D, Hoehn H, Hentze S, *et al.* Comparative evaluation of diepoxybutane sensitivity and cell cycle blockage in the diagnosis of Fanconi anemia. *Blood* 1995;85:2233-7.
70. Shimamura A, de Oca RM, Svenson JL, Haining N, Moreau LA, Nathan DG, *et al.* A novel diagnostic screen for defects in the Fanconi anemia pathway. *Blood* 2002;100:4649-54.
71. Gutiontov SI, Shin EJ, Lok B, Lee NY, Cabanillas R. Intensity-modulated radiotherapy for head and neck surgeons. *Head Neck* 2016;38(S1):E2368-73.
72. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, *et al.* Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): An open-label randomized controlled phase 3 trial. *Lancet* 2019;393:51-60.
73. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004;77:257-67.
74. Scheckenbach K, Morgan M, Filger-Brillinger J, Sandmann M, Strimling B, Scheurle W, *et al.* Treatment of the bone marrow failure in Fanconi anemia patients with danazol. *Blood Cells Mol Dis* 2012;48:128-31.
75. Rio P, Navarro S, Bueren JA. Advances in gene therapy for Fanconi anemia. *Hum Gene Ther* 2018;29:1114-23.
76. Sharma P, Sharma N, Sharma D. A narrative review on Fanconi Anemia: Genetic and diagnostic considerations. *Glob Med Genet* 2022;9:237-41.
77. Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: A review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2009;23:233-48.
78. Mehta PA, Ebens C. Fanconi Anemia Synonym: Fanconi Pancytopenia. United States: National Center for Biotechnology Information, US National Library of Medicine.
79. Alter BP, Caruso JP, Drachtman RA, Uchida T, Velagaleti GV, Elghetany MT. Fanconi anemia: Myelodysplasia as a predictor of outcome. *Cancer Genet Cytogenet* 2000;117:125-31.
80. Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, de Die-Smulders C, *et al.* Biallelic inactivation of BRCA2 in Fanconi anemia. *Science* 2002;297:606-9.
81. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med* 2008;359:2143-53.
82. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet* 2008;40:17-22.
83. Lancaster JM, Wooster R, Mangion J, Phelan CM, Cochran C, Gumbs C, *et al.* BRCA2 mutations in primary breast and ovarian cancers. *Nat Genet* 1996;13:238-40.
84. Kennedy RD, D'Andrea AD. The Fanconi Anemia/BRCA pathway: New faces in the crowd. *Genes Dev* 2005;19:2925-40.
85. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, *et al.* Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009;361:123-34.
86. Liu W, Palovcak A, Li F, Zafar A, Yuan F, Zhang Y. Fanconi anemia pathway as a prospective target for cancer intervention. *Cell Biosci* 2020;10:39.
87. Ghosh A, Ghosh S, Maiti GP, Mukherjee S, Mukherjee N, Chakraborty J, *et al.* Association of FANCC and PTCH1 with the development of early dysplastic lesions of the head and neck. *Ann Surg Oncol* 2012;19(Suppl 3):528-38.
88. Szaumkessel M, Richter J, Giefing M, Jarmuz M, Kiwerska K, Tönnies H, *et al.* Pyrosequencing-based DNA methylation profiling of Fanconi anemia/BRCA pathway genes in laryngeal squamous cell carcinoma. *Int J Oncol* 2011;39:505-14.
89. Hess CJ, Ameziane N, Schuurhuis GJ, Errami A, Denkers F, Kaspers GJ, *et al.* Hypermethylation of the FANCC and FANCL promoter regions in sporadic acute leukemia. *Anal Cell Pathol* 2008;30:299-306.