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The Fanconi Anemia and Breast Cancer Susceptibility Pathways

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Abstract

The study of rare genetic diseases can lead to insights into the cause and treatment of common diseases. An example is the rare chromosomal instability disorder, Fanconi Anemia (FA). Studies of this disease have elucidated general mechanisms of bone marrow failure, cancer pathogenesis, and resistance to chemotherapy. The principal features of FA are aplastic anemia in childhood, susceptibility to cancer or leukemia, and hypersensitivity of FA cells to DNA cross-linking agents. There are thirteen FA genes, and one of these genes is identical to the well known breast cancer susceptibility gene, *BRCA2*. The corresponding FA proteins cooperate in the recognition and repair of damaged DNA. Inactivation of FA genes occurs not only in FA patients but also in a variety of cancers in the general population. These findings have broad implications for predicting the sensitivity and resistance of tumors to conventional anti-cancer agents, to inhibitors of poly-ADP ribose polymerase 1, an enzyme involved in DNA repair, and to other inhibitors of DNA repair.

Fanconi Anemia (FA) is a rare chromosome instability syndrome characterized by aplastic anemia in childhood, susceptibility to leukemia and cancer, and hypersensitivity of FA cells to interstrand DNA crosslinking agents, such as cisplatin and melphalan¹⁻⁴. Treatment of cultured FA cells with such agents increases chromosome breakage,⁵⁻⁷ a phenomenon that is the basis for the definitive diagnostic test. There are thirteen FA genes (Table 1)³, and the inheritance pattern is autosomal recessive for all FA subtypes except for one, which is X-linked recessive. The FA proteins fall into several classes of enzymes and structural proteins, including a ubiquitin ligase⁸; monoubiquitinated proteins;^{9, 10 11 12} a helicase;¹³⁻¹⁵, and one with both helicase and nuclease motifs¹⁶ (see Supplemental Figure 1).

Surprisingly, one of the FA proteins is also the breast/ovarian cancer susceptibility protein *BRCA2*, and is referred to here as *FANCD1/BRCA2*¹⁷. FA proteins and another breast/ovarian cancer susceptibility protein, *BRCA1*, cooperate in a DNA repair pathway which is required for resistance to DNA interstrand crosslinks¹⁰. Recent studies indicate that *FANCD1/BRCA2* and *BRCA1* interact through a binding interaction with another FA protein, *FANCN/PALB2*^{18,19}. Furthermore, molecular and functional interactions of FA proteins with additional proteins responsible for other DNA repair disorders²³ suggest a common pathogenesis for all of these rare chromosome instability disorders.

Germline mutations in FA genes occur in FA, but somatic mutations and epigenetic silencing of these genes occur in a variety of cancers in the general population (non-FA patients)²⁴⁻²⁸. A defect in DNA repair is a mechanism of genomic instability in cancer and may underlie the sensitivity of cancer cells to certain types of chemotherapeutic drugs. For

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this reason, disruption of FA genes is a useful predictor of sensitivity to chemotherapy with DNA crosslinking agents (cisplatin, mitomycin C, and melphalan),²⁹ or with inhibitors of DNA repair (³⁰⁻³³).

Clinical Course of FA

The main clinical features of FA are multiple congenital abnormalities, bone marrow failure, and susceptibility to cancer.¹ The prevalence of FA is 1-5/10⁶, and the heterozygous carrier frequency is about 1 in 300. The median age at diagnosis is 6.5 years for boys and 8 years for girls, but the age at diagnosis ranges from 0 to 48 years. From 1981 to 1990, the median age at death was only 19 years; by 2000 the median age had reached 30 years, probably because of improved medical care. The common congenital defects include short stature (51%), abnormalities of the skin (55%), arms (43%), head (26%), eyes (23%), kidneys (21%), ears (11%) and developmental disability (11%). About 25%-40% of FA patients are physically normal.

Bone marrow failure typically develops during the first decade of life.³⁴ The actuarial risk of marrow failure is 90% by 40 years of age³⁵. In at least 20% of FA patients malignancies also develop;^{35,36} of these, acute myelogenous leukemia is the most frequent. Other tumors include head and neck squamous cell carcinoma, gynecological squamous cell carcinoma, esophageal carcinoma, and liver, brain, skin and renal tumors.

Diagnosis and Treatment

Exposure of FA cells to DNA cross-linking agents, such as diepoxybutane (DEB), increases chromosome breakage and causes marked accumulation of cells in the G2 phase of the cell cycle. The DEB-induced chromosome breakage assay (DEB test) is widely used as a diagnostic test for FA⁵⁻⁷. FA sub-typing (determination of the complementation group) has become increasingly important,^{37,38} as there is some variation in the clinical course, depending on the FA subtype³⁵. The FA-D1 subtype is associated with a predisposition to medulloblastoma, Wilms tumor, and acute leukemia in early childhood. To confirm the diagnosis, distinguish FA from other chromosome breakage disorders, and best manage each patient and the family, FA sub-typing should be routine. Cell fusion assays are useful for sub-typing, but a combination of retroviral gene transfer and a G2 accumulation assay, or a combination of retroviral gene transfer and immunoblotting to detect the FANCD2 protein, are also useful³⁹.

Androgens and hematopoietic growth factors can be effective for treating the bone marrow failure of FA, but most patients become refractory to these treatments. For these patients, hematopoietic stem cell transplantation is possible, provided a donor is available. Pre-implantation Genetic Diagnosis (PGD) is a new approach for identifying potential sibling donors for FA patients⁴⁰. Autologous bone marrow transplantation that entails gene therapy or induced pluripotent stem cells (IPS cells) may become options^{41 42}. The prevention, surveillance for, and treatment of solid tumors is important in management.

The Fanconi Anemia Proteins in a DNA Repair Pathway

The identification of thirteen discrete complementation groups in FA led to the cloning of the FA genes and the analysis of FA proteins. Since FA patients share a characteristic clinical and cellular phenotype, it has been assumed that the thirteen FA proteins cooperate in a common DNA repair pathway. Indeed, the FA proteins work in concert to control the monoubiquitinated state (the addition of one ubiquitin, a seventy-six amino acid tag, to the internal lysine residue of a protein) of the FANCD2 and FANCI proteins (Figure 1) and the

downstream functions of the pathway. DNA damage or entry into the S phase of the cell cycle activates monoubiquitination .

Eight of the FA proteins assemble into a nuclear ubiquitin E3 ligase complex (FANCA/B/C/E/F/G/L/M) known as the FA core complex. This complex monoubiquitinates FANCD2 and FANCI,^{43,11, 44} thereby altering their subcellular distribution. The ubiquitin-tagged FANCD2/FANCI complex moves to chromatin, where it assembles in nuclear DNA repair foci. In these foci, the protein complex interacts with other downstream FA proteins (FANCD1, FANCN, and FANCI) and additional DNA repair proteins. The monoubiquitinated FANCD2/FANCI complex may have a ubiquitin binding partner, which allows the complex to bind stably to damaged chromatin. The downstream FA proteins play an important role in repair by homologous recombination (the exchange of nucleotide sequences between two similar or identical strands of DNA), thereby linking the whole pathway to a common DNA repair mechanism. A ubiquitin-specific protease, USP1, removes the ubiquitin from the FANCD2/FANCI complex;⁴⁵⁻⁴⁷ genetic disruption of USP1 in model organisms yields an FA phenotype,^{48, 49} suggesting that ubiquitination and loss of ubiquitin by FANCD2 are equally important to the function of the pathway.

The FA pathway in normal cells is not constitutively active, but is turned on during the S phase of the cell cycle or following DNA damage. A critical event is phosphorylation of FA proteins, which occurs by the action of the damage-response kinases ATM and ATR. Abnormalities of the *ATM* and *ATR* genes cause ataxia telangiectasia²⁰ and Seckel syndrome²³, respectively. These chromosome instability disorders are related to FA. The FANCM and FAAP24 proteins, which anchor the FA core complex to the damaged DNA, may be an early step in recognizing DNA damage^{50, 51}. The FANCM/FAAP24 complex may have multiple functions in DNA repair systems or in suppressing some recombination events during mitosis.⁵²⁻⁵⁶ Although mutations in the thirteen FA genes account for most, if not all, cases of FA, additional genes related to the FA pathway have been found. Knockdown of certain gene products, such as the novel E2 ubiquitin conjugating enzyme, UBE2T, the USP1 enzyme, and the USP1-binding protein, UAF1⁴⁶, also disrupt the FA pathway, and cause hypersensitivity to DNA cross-linking agents.

Possible Functions of the FANCD2 protein

Despite many studies of the regulation of ubiquitination of FANCD2 and FANCI^{10,11, 57}, the downstream function of the ubiquitinated FANCD2/FANCI complex (Figure 2) remains unknown. The complex is required for efficient activation of downstream FA molecules, and it may contribute to homologous recombination, perhaps by directly binding to DNA⁵⁸. The FANCD2/FANCI complex may also serve as a “landing pad” for a new DNA repair factor, such as a DNA polymerase that can replicate past the damaged DNA base. A very recent report indicates that the FANCD2/FANCI complex can execute one or more of these functions⁵⁹.

An intriguing manifestation of FA cells is their reduced ability to develop point mutations in response to DNA crosslinks^{60, 61, 62}. Instead, these cells display large chromosomal insertions and deletions. The FA pathway may therefore facilitate an error-prone repair process that causes point mutations while protecting cells from gross chromosomal rearrangements. The predominant mechanism for generating point mutations is through error-prone DNA polymerases (TLS polymerases), making it likely that the FANCD2/FANCI complex interacts, either directly or indirectly, with one of these polymerases⁵⁹.

The Fanconi Anemia D1 gene (*FANCD1*) and the Breast Cancer Susceptibility Gene *BRCA2*

That the Fanconi anemia gene *FANCD1* is identical to the breast cancer susceptibility gene *BRCA2* was a surprising and unifying discovery¹⁷. Several observations set the stage for this finding. First, heterozygote carriers of a *BRCA2* mutation have a high risk of breast, ovarian, or pancreatic cancer (^{63, 64, 65}). The tumors in heterozygotes result from loss of the second (wild type) *BRCA2* allele, resulting in biallelic extinction of *BRCA2*. *BRCA2* (–/–) cells undergo chromosome breakage when exposed to DNA cross linkers and exhibit tri-radial chromosomes, the hallmarks of FA cells⁶⁶. Second, BRCA2 protein co-localizes with monoubiquitinated FANCD2 in nuclear foci induced by DNA damage. Third, BRCA2 is a bona fide DNA repair protein, required for the formation of RAD51 filaments and strand invasion during homologous recombination.⁶⁷ We had suspected that *FANCD1* was involved in repair by homologous recombination, since FA cells are especially sensitive to crosslinking drugs and ionizing radiation. Using a candidate gene approach, we sequenced the *BRCA2* gene in cells derived from FA-D1 patients and their families,¹⁷ and found that the cells had biallelic mutations in *BRCA2* and expressed truncated BRCA2 proteins. Heterozygote (*BRCA2* +/-) members of FA-D1 kindreds, such as parents of children with FA, were found to have an increased risk of breast and ovarian cancer⁶⁸. All these findings merged two previously unrelated fields of medical research, which had in common mechanisms of DNA repair.⁶⁹

The clinical picture of *FANCD1/BRCA2* deficient FA patients is more severe than classical FA subtypes, with earlier onset of embryonal pediatric tumors⁷⁰. The *FANCD1/BRCA2* protein functions downstream in the classical FA pathway and interacts with other FA proteins^{72 73 74}. Other studies have found a relation between the FA pathway and another breast cancer susceptibility gene, *BRCA1*, which encodes a protein that binds to BRCA2⁷⁵. There is now direct evidence that the canonical FA proteins and the *FANCD1/BRCA2* protein can be recruited to sites of DNA interstrand crosslinks⁷⁶. To emphasize the connection between FA and breast cancer, the pathway was renamed the Fanconi Anemia/BRCA pathway⁷⁷ or network^{78, 79}.

Other FA Genes and Breast Cancer Susceptibility Genes

The discovery that the *FANCD1* gene is identical to *BRCA2* brought other FA genes under scrutiny as possible breast cancer risk genes. It was soon found that biallelic mutations in *BRIP1/BACH1* (*FANCF*)³ and *PALB2* (*FANCL*)^{80, 81} cause rare subtypes of FA, namely the FA-J and FA-N subtypes respectively. Patients assigned to the FA-N subtype, whose cells contain biallelic *PALB2* mutations, also have early onset of embryonal pediatric cancers. The PALB2 protein binds directly to the BRCA2/*FANCD1* protein⁸², which may account for the strong clinical resemblance between FA-N and FA-D1 patients. FA-J patients, whose cells contain biallelic mutations in *BRIP1/FANCF*, have a more classical FA phenotype, with bone marrow failure and AML, but a lower incidence of solid tumors. Mutations in *FANCF* (*BRIP1*) have also been identified in patients with early onset breast cancer⁸⁵ although the lifetime risk in carriers of *FANCF* (*BRIP1*) mutations is unknown. Carriers of mutations in *BRCA2/FANCD1* have an elevated lifetime risk of breast cancer^{83 84}. It remains possible that mutations in other breast cancer susceptibility genes may be responsible for still other FA subtypes. FA patients with biallelic mutations in *BRCA1* have not been identified; perhaps biallelic loss of *BRCA1* results in embryonic lethality.

To date, three FA genes (*FANCD1*, *FANCL*, and *FANCF*) have been shown to be bona fide breast cancer susceptibility genes. The sequencing of DNA from members of families with heightened breast cancer risk has not revealed mutations in other FA genes⁶⁴. There have

been occasional reports of cancers in heterozygote carriers from other FA complementation groups ⁸⁶, but since all FA genes cooperate in the same DNA repair pathway, it is unclear why some FA gene mutations impose a higher risk of cancer than others. Recent studies indicate that these three FA proteins related to breast cancer are recruited to the site of a DNA interstrand crosslink by a downstream mechanism requiring DNA replication, but independent of the upstream FA core complex ⁷⁶ (Figure 3).

Cancer Risk in Heterozygous Carriers of FA Gene Mutations

How germline mutations in some FA genes lead specifically to breast and ovarian cancer is unknown. Perhaps estrogen promotes the survival of breast and ovarian cells that have undergone critical DNA damage, whereas apoptosis occurs in other somatic cells with a disrupted DNA repair pathway ⁸⁷. Consistent with this hypothesis is that oophorectomy, which diminishes serum estrogen levels, protects against breast cancer in *BRCA2/FANCD1* mutation carriers ⁸⁸.

Paradoxically, breast or ovarian cancer rarely, if ever, develop in FA patients. Hypogonadism with decreased estrogen levels in FA females may account for this phenomenon. In families carrying a *BRCA2/FANCD1* mutation, the peak age of onset of breast or ovarian cancer among heterozygote carriers is in the fourth decade ⁸⁹, whereas homozygote (*BRCA2* $-/-$) FA patients often die from complications of aplastic anemia well before this age. Taken together, these observations demonstrate that the timing of biallelic loss of *BRCA2* (whether germline loss of both alleles or secondary loss of the second allele later in life) can determine the specific cancer spectrum.⁹⁰.

Heterozygosity for a mutation in *BRCA2/FANCD1* also predisposes to pancreatic cancer. In one study, 19% of families with a history of hereditary pancreatic cancer carried a frameshift mutation or an unclassified variant of *BRCA2/FANCD1* ⁹¹. Other FA gene mutations have also been identified in pancreatic cancer. One recent study determined that 2 out of 400 patients with pancreatic cancer carried a heterozygous germline mutation in *FANCC* ⁸⁶. The pancreatic tumors from these patients exhibited loss of heterozygosity at the *FANCC* locus, indicating a mutation in one allele and deletion of the other. Recent studies have determined that other families with inherited pancreatic cancer carry germline mutations in other FA genes ^{92 93 94}.

Epigenetic Disruption of the FA Pathway

Some human ovarian tumor lines are deficient in monoubiquitination of the FANCD2 protein ⁹⁵, a marker of FA pathway activity, and are also hypersensitive to the crosslinking agent cisplatin. Moreover, transfection of these cells with the *FANCF* cDNA, but not with other *FANCC* cDNAs, complemented their hypersensitivity to cisplatin. The mechanism of disruption of the FA pathway in these cells is silencing of the *FANCF* gene by epigenetic methylation. Moreover, methylation of *FANCF* was found in four of nineteen primary ovarian adenocarcinomas, and this could account, at least in part, for the cisplatin hypersensitivity of these tumors. Methylation of the *FANCF* promoter has been found in 24% of ovarian granulosa cell tumors ⁹⁶, 30% of cervical cancers ⁹⁷, 14% of squamous cell head and neck cancers and 15% of non-small cell lung cancers ⁹⁸. Epigenetic factors affecting the FA pathway may also be important in the development of sporadic leukemia^{99 100}. Recent studies indicate that the prevalence of *FANCF* methylation in some solid tumors may be lower than originally reported ^{101 102 103, 104}.

How methylation and silencing of an FA gene contribute to tumor progression is unknown. An early cancer, could develop a DNA repair defect and chromosome instability due to hypermethylation of a normal FA gene (Figure 4). Additional genetic alterations could

follow. The initial hypersensitivity of a tumor to cisplatin, due to a DNA repair defect, could be negated by demethylation of an FA gene (or selection for tumor cells with reduced gene methylation). Testing for FA gene methylation during tumor progression and during cancer therapy could provide a means of predicting the tumor's sensitivity to chemotherapy. Many laboratories are investigating the prevalence of FA gene methylation in cancer and the value of FA methylation in predicting responsiveness to chemotherapy. In principle, a small molecule that inhibits the FA pathway could reverse resistance to cisplatin, and several approaches are being taken to generate FA pathway inhibitors¹⁰⁵⁻¹⁰⁸. Defects in the FA pathway have been identified in cisplatin-sensitive pancreatic cancer^{26, 27} and glioblastoma cell lines²⁹.

The FA Pathway and Cancer Treatment

Recent studies have indicated that tumor cells with a defect in homologous recombination, such as tumors bearing *BRCA1* or *BRCA2* mutations, depend to a major degree on a compensatory DNA repair process called Base Excision Repair (BER). Poly-ADP ribose polymerase 1 (PARP1) is a critical enzyme for BER. . Consequently, tumors with defects in homologous recombination are hypersensitive to PARP inhibitors^{31, 109, 110, 32,33}. The finding of hypersensitivity to PARP inhibitors in tumor cells with a disrupted FA pathway would expand the utility of PARP inhibitors.¹¹¹⁻¹¹⁴.

Limitations and Perspective

The finding that the FA/BRCA pathway is intimately involved in the response to DNA damage has spurred research in the field of DNA repair. Fundamental questions remain, however. In particular, it is unclear how the loss of a single DNA repair pathway can lead to developmental abnormalities, bone marrow failure, and predisposition to cancer in FA. Also unknown is how deficiency in the FA pathway selectively causes hypersensitivity to DNA crosslinking agents, but not to other forms of DNA damage.

The study of patients with FA has led to the elucidation of a novel DNA repair pathway which is regulated by at least thirteen different genes. Only three of the genes in this pathway (*FANCD1/BRCA2*, *FANCN*, and *FANCI*) appear to function downstream and confer susceptibility to breast cancer . A better understanding of this pathway may lead to better characterization of FA patients into different treatment groups and improved assessment of the cancer risk of individual FA patients and heterozygote FA family members.

Abnormalities in the FA/BRCA pathway are found not only in childhood Fanconi Anemia but also in sporadic cancers in the general (non-FA) population. On the one hand, somatic disruption of FA genes, resulting from epigenetic silencing, can fuel genomic instability and cancer progression. On the other hand, such somatic mutation may render these sporadic tumors more sensitive to conventional anti-cancer therapy (i.e, cytotoxic chemotherapy and radiation). It will also be interesting to determine whether inherited polymorphisms in FA genes, resulting in more subtle defects in FA protein expression or FA protein function, can contribute to increased cancer risk or to variable tumor responses to conventional therapies.

A better understanding of the FA pathway may allow the development of strategies to correct the pathway, thus preventing carcinogenesis in FA patients or those carrying a heterozygous mutation. In some cases, antioxidant therapy may be useful in delaying the onset of bone marrow failure or cancer¹¹⁷. Inhibitors of the pathway may be used as sensitizers to crosslinking chemotherapeutic agents in cancer treatment¹⁰⁵. It is evident that a better understanding of this complex pathway remains a priority for future medical research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

Ubiquitin	A 76 amino acid tag which is added to proteins post-translationally
Monoubiquitinate	To add one ubiquitin to the internal lysine residue of a protein
Deubiquitinate	To enzymatically remove a ubiquitin from a protein
Ubiquitin Ligase	An enzyme that can add a ubiquitin to a protein
Helicase	An enzyme that can separate the strands of a DNA double helix using the energy of ATP hydrolysis
Homologous Recombination Repair	A DNA repair pathway that can repair a double strand break

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Figure 1. Schematic of the Fanconi anemia DNA repair pathway

After DNA damage, the Ataxia Telangiectasia and Rad3-related kinase (ATR) activates FA core complex (FANCA/B/C/E/F/G/L/M). The FA core complex then functions as an E3 ubiquitin ligase and monoubiquitinates FANCD2 and FANCI. The Monoubiquitinated FANCD2/FANCI complex is then targeted to chromatin where it forms complex with additional FA proteins and other DNA repair proteins. The USP1 and UAF1 protein complex then deubiquitinates FANCD2/FANCI complex, allowing their release from chromatin. USP1 is also required for localization of FANCD2/FANCI into DNA repair foci.

Figure 2. A simplified model of FA-mediated crosslink repair involving nucleotide excision repair (NER), translesion synthesis (TLS), and homologous recombination (HR)

1) According to this model, the replication fork arrests at a DNA crosslink. The stalled fork is detected by the FA complex, thereby activating the assembly of the monoubiquitinated FANCD2/FANCI heterodimer. The heterodimer stabilizes the arrested fork. Recent studies also indicate that the heterodimer allows DNA strand incision and lesion bypass by the replication machinery 2) NER incises one side of the crosslink leaving a single strand DNA break on one strand and a monoadduct on the opposite strand. 3) The heterodimer recruits a TLS polymerase which bypasses the remaining monoadduct. 4) NER excises the monoadduct. 5) FA pathway mediated HR finally repairs the double strand DNA break. 6) Intermediate DNA cross over structures are resolved and the replication fork is reestablished, a process that may require FA pathway-associated DNA helicases.

Figure 3. The downstream FA proteins, FANCD1, FANCN, and FANCI interact in a common protein complex with BRCA1 to coordinate Homologous Recombination (HR) Repair
 According to this model, the D2/I complex is monoubiquitinated by the FA core complex (not shown). The Ubiquitinated complex then recruits three downstream FA proteins (D1, N, J), which are also breast cancer susceptibility proteins. These three FA proteins form a complex with BRCA1. Recent studies indicate that the PALB2/FANCN protein provides interaction surfaces with both D1/BRCA2 and BRCA1, as drawn (see references ¹⁸ and ¹⁹).

Figure 4. Methylation of the FANCF gene during ovarian tumor progression

According to this model, early in the course of ovarian cancer, the FANCF gene is methylated, leading to chromosome instability. Chromosome instability allows for the inactivation of other tumor suppressor genes, by loss of heterozygosity (LOH), and the generation of new fusion oncogenes. The tumor is hypersensitive to cisplatin, but, after cisplatin exposure, the tumor reemerges as a cisplatin resistant tumor with unmethylated FANCF. Theoretically, an inhibitor of the FA/BRCA pathway may re-sensitize the relapsed tumor to cisplatin.

Table 1

The Thirteen Fanconi Anemia Genes

FA Genes	Prevalence	Chromosomal Position	Protein Size (kDa)	Activity
FANCA	66%	16q24.3	163	Core complex member; required for FANCD2/I ubiquitination
FANCB	2%	Xp22.31	95	Core complex member; required for FANCD2/I ubiquitination
FANCC	10%	9q22.3	63	Core complex member; required for FANCD2/I ubiquitination
FANCD1	2%	13q12-13	380	HR mediator; FANCN interactor; downstream
FANCD2	2%	3q25.3	155, 162	Ubiquitinated following DNA damage
FANCE	2%	6p21-22	60	Core complex member; required for FANCD2/I ubiquitination; binds directly FANCD2
FANCF	2%	11p15	42	Core complex member; required for FANCD2/I ubiquitination
FANCG	9%	9p13	68	Core complex member; required for FANCD2/I ubiquitination
FANCI	< 2%	15q25-26	140, 147	Ubiquitinated following DNA damage
FANCL	< 2%	17q22-24	140	Helicase; BRCA1 interactor; downstream
FANCL	0.2%	2p16.1	43	Core complex member; required for FANCD2/I ubiquitination; ubiquitin ligase activity
FANCM	0.2%	14q21.3	250	Helicase; localizes the core complex to DNA; required for FANCD2/I ubiquitination
FANCN	< 2%	16p12.1	140	FANCD1 and BRCA1 interactor; downstream