Chapter

# Inherited Bone Marrow Failure and Chromosome Instability Syndromes and their Cancer Predisposition

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## Abstract

Inherited bone marrow failure syndromes (IBMFS) and chromosome instability syndromes (CIS) are the most classic and representative genetic syndromes. They are classified as genetic rare diseases, typically with complex medical complications in the delay of mental and physical development. Commonly, these syndromes present with different degrees of dysmorphics; organs/systems dysfunction generally and these syndromes have higher risk of inherited solid cancer and leukemia predisposition due to the similar pathway of DNA defects. These syndromes are often hard to diagnose and they overlap with their phenotypes clinically. Very importantly cancers from the germ line mutation of these syndromes require different treatment strategies with the sporadic malignancies. The significance of recognition of such diseases is not only beneficial to patients phenotypically affected but also to individuals phenotypically unaffected and members/relatives of the family. Remarkable advances have been made in the definition and classification of these genetic syndromes. Identification of the IBMFS and CIS has led to important advances in the understanding of the genotypes, guiding the clinical practice of the phenotypes. Interestingly, such studies provided insights into the function of the various DNA repair pathways. Fanconi anemia studies are an example in IBMFS and CIS is named as the paradigm of the studies of cancer and aging.

**Keywords:** inherited bone marrow failure syndromes, chromosomal instability syndromes, genetic rare syndromes, cancer predisposition, cancer prone human syndromes

## 1. Introduction

Bone marrow failure is the term for the activity or function in the bone marrow production of blood cells from the hematopoietic cells. Studies demonstrated that there are more than 80 causative genes identified from bone marrow failure disorders but still about 40% of the disease cause is unidentified. Bone marrow failure disorders are classified into idiopathic (acquired) and inherited-(IBMFS) due to the inherited conditions transmitted in autosomal recessive pattern [1, 2].

There are more than 30 different types of disorders, classified into inherited bone marrow failure syndromes. The common types are Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, Congenital amegakaryocytic thrombocytopenia, Severe congenital neutropenia and thrombocytopenia absent radii [3, 4].

There is another group of syndromes named as chromosomal instability syndromes (CIS), are also known as chromosomal breakage syndromes, typically transmitted in an autosomal recessive pattern of inheritance defined on the basis of cell culture in vitro. The affected individuals exhibit elevated rates of chromosomal breakage or instability, leading to chromosomal rearrangements. CIS often lead to an increased tendency to develop certain types of malignancies as well [5, 6]. Individuals with IBMFS and CIS are commonly in children and these disorders are often lethal.

Relatively high rates of some types of IBMFS and CIS can occur in certain ethnic groups. Diagnosis is usually complicated because the symptoms presented from individuals with IBMFS and CIS may be varied and are often very complex. So practically the differential diagnosis of these two groups of syndromes clinically can be very difficult because they share some characteristics of overlapping phenotypes.

Studies on IBMFS and CIS for better therapies have achieved exciting successes, not only beneficial to IBMFS and CIS studies self but also beneficial to other diseases. One of the IBMFS and CIS, Fanconi anemia, is the disease which achieved a success in stem cell transplantation used umbilical blood in 1988 [7]. This revolutionary treatment has been using as an effective therapy for many different types of diseases, commonly in malignancies in clinical application since then. Studies found that the majority of IBMFS and CIS are associated with cancers from the germ line mutation and such studies have explored many mysteries in cancer research. For example, Fanconi anemia is found to associate with many different types of cancers from those mutated genes [8].

Recent advances in molecular-based studies on the identification of responsible genes and defects in their pathways of IBMFS and CIS have provided more understanding in the pathophysiological mechanisms. Such advances also provided the link between IBMFS/CIS and some types of cancers in the genetic defective pathways. Results obtained from research showed that human cancer is caused of genetic and environmental factors and their interactions in general. Cancers fall into the genetic disease category due to two genetic factors: (1) acquired somatic mutations produced by genomic instability and (2) inherited gene mutations. The important difference between familial/inherited and sporadic cancer is due to the form of germ line mutation in a DNA caretaker gene facilitating the accumulation of oncogenic DNA changes, which can result in a high susceptibility to cancer. Both IBMFS and CIS have cancer predisposition commonly in AML and MDS, often diagnosed at a young age. These types of malignancies require different treatment strategies due to the underlying gene defects.

To increase the recognition of myeloid leukemia/MDS associated with inherited or germ line mutations, a major change has been made by adding the germ line mutation in the classification of myeloid neoplasms and acute leukemia in the new version of classification of tumors of the hematopoietic and lymphoid tissues published by the World Health organization (WHO) in 2016 including (1) myeloid neoplasms with germ line predisposition without a pre-existing disorder or organ dysfunction, (2) myeloid neoplasms with germ line predisposition and pre-existing platelet disorder and (3) myeloid neoplasms with germ line predisposition and other organ

dysfunction. Similarly, studies demonstrated that hereditary predisposition has a higher risk of development of acute lymphoblastic leukemia (ALL) as reported in TP53 [9].

Recently, studies on genetic disease by the modern technologies, particularly by the next generation sequencing dramatically increased the understanding of the etiology and classification of IBMFS. So more and more mutated genes have been identified and these studies demonstrated that genomic instability, defects in DNA repair and telomere biology are the genetic causes. Such discoveries have provided insights into several biological pathways, correlation between phenotype and genotype, and clinical therapeutically strategies.

In this chapter, the aim IS to review and discuss IBMFS and CIS, together with comparison of their phenotypes and genotypes. It is hoped that review will increase understanding in further translation of research to clinical practice, so as to raise awareness of these genetic-based diseases and the impact on patients' lives as well as improvement of the therapies.

## 2. The common types of IBMFS

IBMFS are a heterogeneous group of complex genetic disorders characterized by bone marrow failure, commonly associated with one or more somatic abnormalities and increased cancer risks in childhood but also in adulthood.

The common and representative types of IBMFS are Fanconi anemia, Dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, Congenital Amegakaryocytic thrombocytopenia, Severe congenital neutropenia and thrombocytopenia absent radii. The phenotype and genotype of IBMFS and their association are summarized in **Table 1**.

### 2.1 Fanconi anemia

Fanconi anemia (FA) is a hereditary disorder with defects in DNA repair and is usually inherited as an autosomal recessive trait but it can be X-linked (FA

| Syndromes | Inheritance | Somatic abnormalities | Bone marrow failure | Short telomeres | Cancer risk | Identified gene numbers | References |
|---|---|---|---|---|---|---|---|
| FA | AR/XLR | Yes | Yes | Yes | Yes | 22 | [10, 78] |
| DC | AD/AR/XLR | Yes | Yes | Yes | Yes | 9 | [26, 27] |
| SDS | AR | Yes | Yes | Yes | Yes | 1 | [28, 29] |
| DBA | AD | Yes | Yes | Yes | Yes | 11 | [31, 32] |
| SCN | AD/AR | Yes | Yes | ? | Yes | 5 | [36, 38] |
| CAMT | AR | Yes | Yes | ? | Yes | 1 | [39, 40] |
| TAR | AR | Yes | Yes | ? | Yes | 1 | [41, 42] |

*FA, Fanconi anemia; DC, dyskeratosis congenita; SDS, Shwachman-Diamond syndrome; DBA, Diamond Blackfan anemia; CAMT, congenital amegakaryocytic thrombocytopenia; SCN, severecongenital neutropenia; AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.*

**Table 1.**
*Common types of inherited bone marrow failure syndromes.*

| Complementation groups | Gene's symbols | Locations on chromosomes |
|---|---|---|
| FA-A | FANCA | 16q24.3 |
| FA-B | FANCB | Xp22.31 |
| FA-C | FANCC | 9p22.3 |
| FA-D1 | FANCD1 | 13q12.3 |
| FA-D2 | FANCD2 | 3p25.3 |
| FA-E | FANCE | 6p21.3 |
| FA-F | FANCF | 11p15 |
| FA-G | FANCG | 9p13 |
| FA-I | FANCI | 15q26.1 |
| FA-J | FANCJ | 17q22 |
| FA-L | FANCL | 2p16.1 |
| FA-M | FANCM | 14q21.3 |
| FA-N | FANCN | 16p12 |
| FA-O | FANCO | 17q25.1 |
| FA-P | FANCP | 16p13.3 |
| FA-Q | FANCQ | 16p13.12 |
| FA-R | FANCR | 15q15 |
| FA-S | FANCS | 17q21 |
| FA-T | FANCT | 1q32.1 |
| FA-U | FANCU | 7q36 |
| FA-V | FANCV | 1p36 |
| FA-W | FANCW | 16q22.3 |

*Data extracted from the Rockefeller University » Fanconi Anemia Mutation. Database at www.rockefeller.edu/fanconi, Ref. [10].*

**Table 2.**
*Fanconi anemia genes and locations on chromosomes.*

complementation group B). Cells from patients with FA are more sensitive to chemotherapy than those from patients without FA, which can cause severe consequences from the normal dose of chemotherapies. So far, 22 genes responsible for FA have been identified [10]. In the general population, the complementation A occurs in about 60–70%, while complementation-C occurs in about 15% and the complementation-G occurs in about 10% of the total 22 FA responsible genes mutated with a vary of their subgroups in some geographical regions (**Table 2** and **Figure 1**).

Patients with FA are characterized with congenital abnormalities but progressive bone marrow failure is the most common characteristic, so it is named as IBMFS. FA also increases susceptibility to malignancies and individuals with FA also can suffer one or more types of cancers.

FA also has with variable congenital malformations and a predisposition to develop hematological or solid tumors, commonly in MDS, AML, and solid tumors, commonly carcinoma of the oropharynx and skin. Studies found the association of FA with a pattern of recurrent chromosomal abnormalities including monosomy chromosome 7, deletion of the long arm of chromosome 7, gain of the long arms of chromosome 3 and 1 and the RUNX1 gene mutations in about 20% of the combined MDS cases. Chromosome abnormalities with 7 and 3 had a poor prognostic indication value [11].

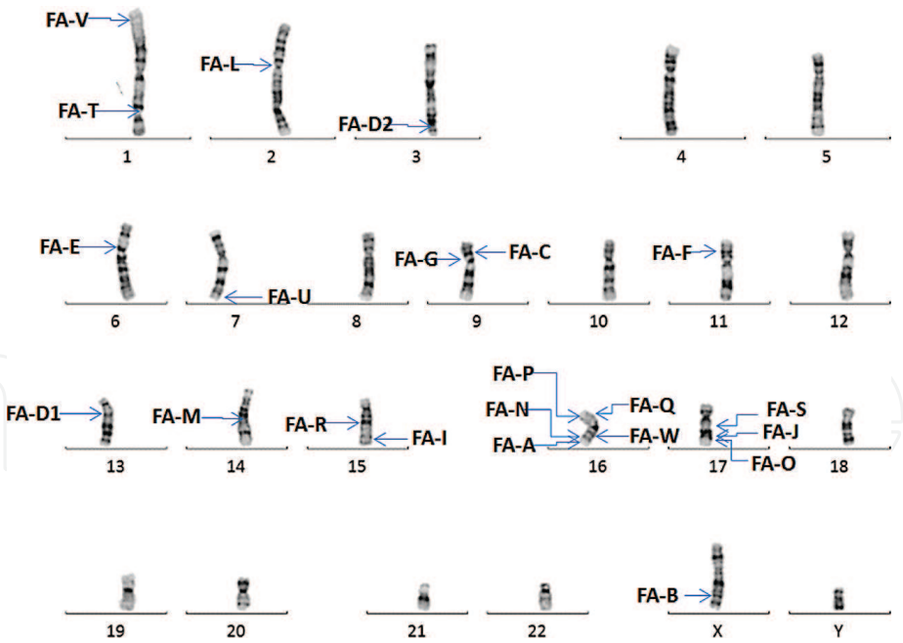


**Figure 1.**
*22 FA-genes identified on chromosome locations constructed from the data extracted from the Rockefeller University Fanconi Anemia Mutation Database at: www.rockefeller.edu/fanconi. Ref. [10].*

The FA pathways are defined from the encoded proteins work in concert in a distinct genomic maintenance. The FA pathways in normal cells are not constitutionally active but they are turned on during the S phase of the cell cycle in the presence of DNA damage to coordinate distinct repair functions in nucleotide excision, translesion synthesis and homologous recombination to remove the cross links [12].

The 22 FA gene products make up the FA pathways in the maintenance of genomic stability and the FA pathways can be activated by DNA damage and replication. The number of FA proteins reflects the complicated nature of the FA pathways. Mutation in any of the 22 FA genes causes defects in the response to DNA damage and repair results in disease of FA by the loss of DNA interstrand cross-links repair [13]. The FA pathways are the key event with the complex pathological mechanisms in DNA repair and cancer suppression in both inherited and sporadic cancers.

The proteins involved in FA consist of several classes of enzymes and structural proteins, including ubiquitin ligase, monoubiquitinated proteins and helicase [14]. FA nuclear core protein complex consists of eight proteins, encoded by FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM, with ubiquitin ligase activity. This protein complex is required for the critical monoubiquitination of FANCD2 and FANCI in response to DNA damage during replication. The biological functions of this protein complex are to maintain DNA stability and repair DNA damage protein-protein interactions are required for core complex protein stability form the stable core protein complex in function that is required for the modification of FANCD2 and FANCI by monoubiquitination.

E3 ubiquitin-protein ligase FANCL belongs to the multi-subunit FA complex and is a ligase protein that mediates monoubiquitination of FANCD2, a key step in the repair of ICLs in the FA pathways [15]. FANCL is associated with hypersensitivity to DNA-damaging agents, chromosomal instability (increased chromosome breakage) and defective DNA repair [16]. The monoubiquitination process of FANCD2 and FANCI recruits DNA repair machinery in order to maintain genomic integrity during cellular proliferation within certain tissues. Mutation in any member

of a core protein complex results in the loss of the monoubiquitination of the FANCI/FANCD2 complex step [17]. FANCD2 and FANCI proteins are substrates for ubiquitination with the two being similar in size and domain structure. This monoubiquitination is the crucial event of the FA pathways, and the monoubiquitination isoform of FANCD2 associates with the repair protein BRCA1 in DNA damage-induced nuclear foci. This foci formation is induced by both cross-linking agents and DNA-damaging agents and this process is regulated by the nuclear core protein complex [18].

The genetic association between cancers with FA and without FA gene mutation clinically has been intensively investigated and a close connection has been discovered between FA and tumorigenesis observed from both clinical and cellular phenotypes. Inherited homozygous (bi-allelic) mutations from germ line can cause FA phenotype and increase susceptibility to both hematologic and non-hematologic malignancies [19]. The first case of FA was recognized as a cause of Juvenile leukemia in 1967 [20]. Cancers with FA gene mutations are difficult to be treated (except surgically) because cells from patients with FA are more sensitive to chemotherapy and radiation comparing with non-FA cancers [21]. The relative risk of non-hematologic malignancies in patients with FA is increased commonly for squamous cell carcinomas (700 times greater than in normal population) including the head and neck, vulva, esophagus, gastric osteogenic sarcoma, cervix and skin. Many other types of cancers including breast cancer, lung cancer, colon cancer and brain tumor were found from patients with FA as well, with the median onset age of cancers being 16 years old in FA patients compared with 68 years in the non-FA population [22]. In addition, FA patients could develop different types of cancers.

The risk of developing to acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) has been reported to increase by 785-fold [23, 24]. It is estimated that acute myeloid leukemia from the germ line mutation associated cause is about 10–15% and it could be higher. Inherited germ line mutations are present in an increasing proportion of children, predisposing them to leukemia. Several genetic syndromes have been found to associate with leukemia/cancers and the best examples are IBMFS and CIS. The risk of leukemia/cancers and the outcome of these syndromes particularly in these with substantial proportion of patients with therapy related leukemia/cancer harbor germ line mutations in DNA damage and response genes such as BRCA1/2 and TP53.

To deal with germ line mutated leukemia, not only requires an increase in awareness of germ line mutations but also taking family history from patients and offering genetic counseling for the relevant to malignant diagnosis, it also requires an understanding of the developments of the genetic landscapes because the treatment strategy for IBMFS and CIS associated malignancies is different from the malignancies in the sporadic manner. The differential diagnosis on malignancies such as MDS, acute leukemia and solid tumors is imperative.

Studies showed that there was no increase of cancer risk from FA carriers in overall but there was evidence that these carriers from FANCC type mutation increase breast cancer risk, so it was suggested that carries of relatives of FANCC should carefully follow the recommendations for breast cancer screening [25].

However, an early and accurate diagnosis for FA is often difficult because FA is a genetically and phenotypically heterogeneous disease lacking specific and typical clinical features. Diagnosis in more or less cases can be delayed until bone marrow failure or cancer/leukemia occurs. As a result, Delayed or misdiagnosis or even wrong treatment received for patients with FA are not uncommon events clinically in some regions or countries due to the lack of recognition of FA from the clinicians and the limitation in testing resource in laboratory.

### 2.2 Dyskeratosis congenita

Dyskeratosis congenita (DC or DKC) is an inherited disease in autosomal dominant, autosomal recessive and X-linked patterns which is defined as one of the IBMFS characterized by the presence of bone marrow failure and the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia [26]. Patients with DC increases the risk of MDS, AML and other types of cancers (carcinomas of the upper gastro-intestinal tract). Aplastic anemia, MDS and AML from patient with DC could be the early or first signs to be seen clinically. DC is the most typical representative type in IBMFS in telomere abnormality causing genomic instability due to the accelerated telomere shortening to result in cell loss or dysfunction and nine genes responsible for DC (DKC1, TERT, TERC, TINF2, RTEL1, NOP10, NHP2, WRAP53 and CTC1) the functioning and maintenance of telomeres have been identified so far [27].

### 2.3 Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder characterized by early onset exocrine pancreatic insufficiency, bone marrow failure and other genetic abnormalities. About 20% of SDS patients will develop MDS and 25% of patients with SDS will develop leukemia [28]. Deletion 5q, monosomy/deletion of chromosomal 7q and 20q are the most frequent abnormalities in patients with SDS presenting with MDS but such types of chromosomal abnormalities do not contribute to leukemia transformation. Molecular studies showed about 90% of SDS patients have SBDS gene mutation and its product has an important role in the maturation of the 60S ribosomal subunit [29].

### 2.4 Diamond-Blackfan anemia

Diamond-Blackfan anemia (DBA) is a rare, dominantly inherited syndrome characterized by bone marrow failure, birth defects, and a significant predisposition to cancer. The main clinical characteristics of DBA are the early infant anemia selectively in erythroid lineage (pure red cell aplasia) with some somatic abnormalities such as craniofacial thumb, cardiac and urogenital malformations [30] commonly develop to an increased predisposition to MDS, AML and other types of tumors has been reported [31]. DBA gene (RPS19) was identified in 1999 [32].

Subsequent studies found the heterozygous mutations in other encoding genes for ribosomal proteins of the small (RPS24, RPS17, RPS7, RPS10, RPS26) and large (RPL5, RPL11, RPL35) ribosomal subunits have also found to associated with DBA and RPS5 gene was found tend to have multiple physical abnormalities [33]. RPS19 mutations causing DBA showed ethnic difference in phenotype expression [34]. Recent studies using aCGH identified deletion of RPL15 as a novel cause of DBA [35].

### 2.5 Severe congenital neutropenia

Severe congenital neutropenia (SCN) is an autosomal recessive disorder characterized by early onset neutropenia and presented with recurrent life infections but early with physical abnormalities. SCN can develop to MDS and AML with the secondary mutations including the granulocyte colony stimulating factor receptor [36]. The neutrophil elastase gene (ELA2), defects in mitochondria gene (HAX1), deficiency in adenylate kinase 2 gene (AK2) and a other genes mutated (GFI1, WASP the transcriptional repressor and the cytoskeletal regulator, respectively) associated with apoptosis was found to responsible for SCN in at least 50% patients

[37, 38]. Such genetic defects in multiple pathways causing congenital neutropenia are in the controlling of granulocytic progenitor differentiation.

### 2.6 Congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is characterized as hemorrhages or bruises associated with thrombocytopenia in infancy but rarely presents with physical defects. MDS and AML but not solid tumors associated with CAMT have been reported [39]. Molecular studies demonstrated the gene mutated called MPL (encoding of the receptor for thrombopoietin) is responsible for CAMT and showed the correlation between genotype and phenotype [40].

### 2.7 Thrombocytopenia absent radii

Studies found that thrombocytopenia absent radii (TAR) can be either in autosomal recessive or de novo pattern, typically seen in infants presenting with thrombocytopenia (low platelet count) and allergy to cow milk, physical characteristic of bilateral absent radii and other types of birth defects [41]. Similarly, acute leukemia and solid tumors have been reported from patients with TAR [42].

The pathological mechanism of thrombocytopenia was studied and the serum level of thrombopoietin (the megakaryocyte growth factor) was increased, suggesting the abnormal differentiation mechanism to megakaryocyte and platelet production [43].

The first molecular finding of interstitial microdeletion at chromosome 1q21.1 containing 10 genes including the TAR responsible gene-RBM8A by using comparative genomic hybridization (CGH) microarray technique was in 2007 [44]. Recent finding proved that RBM8A encodes the conserved Y14 subunit of the exon-junction complex that is essential for RNA processing and expressed in all hematopoietic lineages suggesting the cause of TAR [45].

## 3. The common types of CIS

Studies demonstrated that many types of rare genetic diseases associate chromosome instability typically seen in chromosome instability syndromes with shared clinical features each other. CIS is characterized by an increased frequency of spontaneous or induced chromosomal breaks/aberrations and increased risk of cancer due to the defects of DNA repair as Taylor has defined and described about their clinical features on the most common types of CIS in 2001 [46]. The common cause of chromosomal instability syndromes is the defects of genomic maintenance and DNA repair and they are overlapping and share some clinical features.

The chromosomal instability refers to the predisposition of the chromosomes to undergo rearrangements at the chromosomal level. For example, FA increased spontaneous and inducible chromosome breaks, Ataxia telangiectasia increase chromosome breaks presence of clones with translocations between chromosome 7,14 and X, BLOOM syndrome increased spontaneous and inducible SCE. They are all have increased spontaneous chromatid breaks of symmetrical quadriradials as their main cytogenetic features.

The common types of CIS are FA, Nijmegen breakage syndrome, Ataxia telangiectasia, Ataxia telangiectasia-like disorder and Bloom syndrome. The phenotype and genotype and their association with cancer are summarized in **Table 3**. Interestingly, FA fall into two classes of genetic syndromes: class one is IBMFS which

| Syndromes | Phenotypes | Locations on chromosomes | Mutant genes | Protein functions | Cancer risk | References |
|---|---|---|---|---|---|---|
| Fanconi anemia | Congenital abnormalities, bone marrow failure | Various | FANC-A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T, U, V and W | Various | Yes | [10, 79] |
| Nijmegen Breakage syndrome | Microcephaly and mental retardation, immune-deficiency, radiation sensitivity | 8q21.3 | Nbs1 | BRCT-containing protein | Yes | [52, 79] |
| Bloom's syndrome | Immuno-deficiency, premature aging | 15q26.1 | NLM | DNA helicase | Yes | [57, 78] |
| Ataxia telangiectasia | Neuro-degeneration, immune-deficiency, premature aging, radiation sensitivity | 11q23 | ATM | Protein kinase | Yes | [67, 73] |
| Ataxia telangiectasia-like disorder | Cerebellar degeneration, radiation sensitivity | 11q21 | Mre11 | Exonuclease/ endonuclease | Proposed but no report seen | [74, 77] |

**Table 3.**
*Common types of chromosome instability syndromes.*

has been discussed in the pathogenetic mechanism in the IBMFS part and class two is named as CIS with overlaps in the phenotypes with IBMFS (**Figure 2**).

### 3.1. Fanconi anemia

FA proteins maintain the genomic stability and repair the DNA damaged by factors. But under the condition of FA proteins defects, the damaged DNAs fail to be repaired as normal, resulting in FA clinical phenotypes. Because Fanconi anemia (FA) Cells from FA patients exhibit a hypersensitivity to DNA interstrand cross-linking agents a specific method named "Gold standard" and called "chromosomal fragility testing" using clastogenic agents, mitomycin C (MMC) and diepoxybutane (DEB) was found by Cervenka et al. in 1981 [47] and Auerbach in 1993 [48], respectively The principle of this method is to challenge the hyposensitive FA cells in the cell culture (most commonly T-lymphocytes from peripheral blood) exposed to DEB and MMC and then to analyze the chromosomal aberration, breaks, rearrangements and radials exchanges. A total 50 cells in metaphase are scored and analyzed for chromosomal breakages compared to controls in the same conditions including age and sex. It is positive if the total chromosome breakage is greater

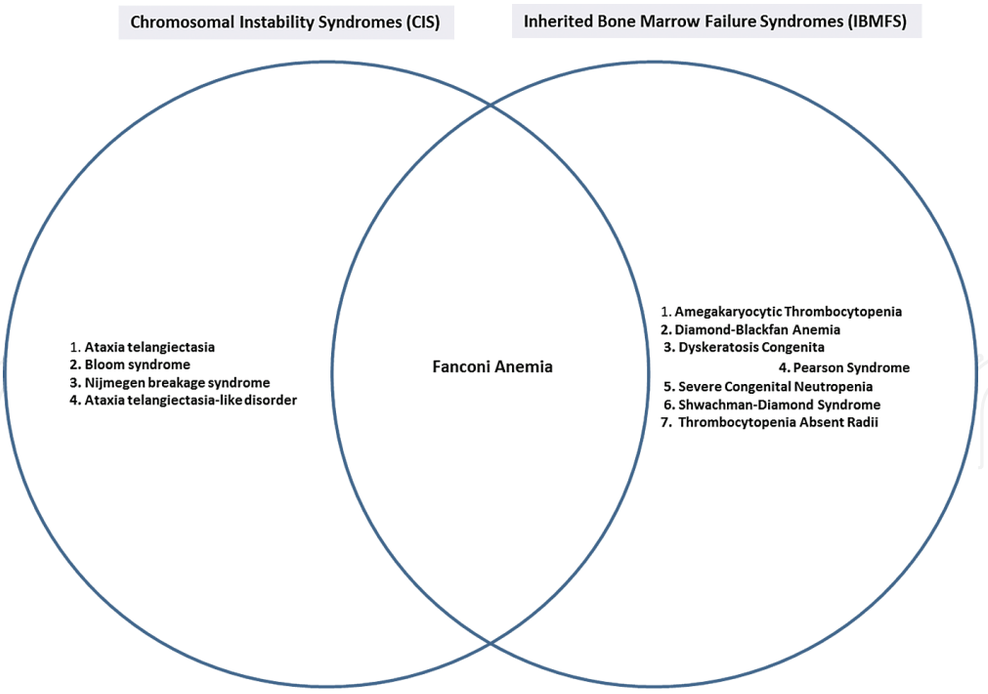


**Figure 2.**
*Major types of CIS and IBMFS. FA overlaps with these two syndromes. Refs. [78, 79].*

than 10-fold comparing to control. A typical chromosome breakage of peripheral lymphocytes induced by MMC from patient with FA is shown in **Figure 3**.

In the last two decades, the method of chromosome fragility testing has been the most widely used as the first line laboratory screen for patients with congenital malformations even without anemia with the features of simple, reliable, reproducible and sensitive comparing with other testing methods in FA diagnosis although it is laborious and requires specialized personnel.

Chromosome fragility test method can differentiate between FA and non-FA cell usually but there are some limitations of this method: (1) it cannot detect the carriers, (2) it is often inconclusive in somatic mosaic cases of FA and (3) false positive results from this test can be seen under the condition that tested individual referred for excluding of FA is under treatment with radiotherapy or chemotherapy

**Figure 3.**
*Chromosomal/chromatid breaks as indicated by arrows induced by MMC from patient with FA.*

in certain period of time. In the earlier times, the spontaneous chromosomal breakage as a marker for FA diagnostic testing was used but it was found the testing result was inconsistent. Spontaneous chromosomal breakage usually indicates a poor prognosis.

The next generation sequencing method for FA testing is to confirm the results found by the chromosomal fragility testing and to identify the specific gene mutations of FA as the severity of the disease and the risk of developing aplastic anemia or malignancies related to the complementation groups. Mutation analysis is to identify the specific gene mutations from the proband after confirmation by the primary complementation group result and molecular techniques.

The conventional Sanger sequencing technology-based mutation sequencing is complicated and time consuming, costly and may not detect all types of disease causing aberrations such as deep intronic mutations, large deletions and amplifications due to the presence of so many mutated genes involved in FA requiring many steps including DNA amplification, sequencing and detection of large deletions. Such testing usually needs to be done in laboratories with specific expertise.

Targeted mutation analysis is used as the clues to detect the common mutations detection. These clues include Ashkenazi Jewish FANCC IVS4 + 4 A>T or FANCD1/BRCA2 6174delT; non-Ashkenazi Jewish Moroccan FANCA 2172-2173insG or FANCA 4275delT; Tunisian FANCA 890-893del; Indian FANCA 2574C>G (S858R); Israeli Arabs FANCA del ex 6-31, FANCA IVS 42-2A>C, and FANCG IVS4 + 3A>G; Japanese FANCC IVS4 + 4 A>T; Afrikaner FANCA del ex 12-31 and FANCA del ex 11-17; Brazil FANCA 3788-3790del; Spanish Gypsy FANCA 295C>T; and Sub-Saharan African Black FANCG 637-643delTAACCGCC [49].

The majority of patients with FA worldwide are the complementation A with several hundred mutations. Deletion/duplication analysis is also used to detect deletions of one or more exons or of an entire gene of any suspected case of FA. So the target sequence analysis is to be used for all the known genes associated with FA which usually is complicated by the number of genes to be analyzed, the large number of possible mutations in each gene, the presence of large insertions or deletions in some genes, and the large size of many of the FA-related genes. If the complementation group has been established the responsible mutation can be determined by sequencing the corresponding gene.

The next generation sequencing (NGS) technology offers exciting promise, an effective and faster molecular diagnostics approach for FA gene studies which is able to perform the mutation analysis for FA genes without the requirement of complementation group testing step which the living cells are required. Ameziane et al. applied the next generation sequencing approach to identify BRCA2, FANCD2, FANCI and FANCL mutations in novel unclassified FA patients [50]. Practical experience proved that NGS is an effective molecular diagnostic approach for IBMFS and CIS, reducing the turnaround tine and the cost gas been becoming lower gradually, and is now a standard tool in the clinical application. Recently, Aslan D group has used the NGS technique and studied a FA case with subtle signs and a negative chromosomal breakage test [51].

In the clinical practice, an early and accurate diagnosis of FA before the stage of bone marrow failure, cancer/leukemia is crucial for the adequate treatment such as stem cell transplantation, the prevention of serious medical complications and also for the properly management in the other caring areas including pediatric, hematology, immunology, endocrinology, reproductive/IVF, obstetrics and surgery and also an early diagnosis of FA will permits the exclusion of other diseases and precludes inappropriate management of hematologic diseases such as aplastic anemia, myelodysplastic syndrome and acute myeloid leukemia.

### 3.2 Nijmegen syndrome

Nijmegen syndrome (NS) is named from the Dutch city Nijmegen where the condition was first described. It is also named Berlin breakage syndrome, Ataxia Telangiectasia variant 1. NS is an autosomal recessive inherited disease with a complex health problematic conditions typically characterized (NS) by short stature, microcephaly, distinctive facial feature, recurrent respiratory tract infections, mental development delay from infancy to childhood, dysfunctional immune deficiency in T cells and low level of immunoglobulin G and A and increased susceptibility to infections. Individuals with NS increased risk of cancer development (>50 times), commonly in Hodgkin lymphoma, brain tumor, rhabdomyosarcoma about 40% of the affected individuals and usual before age 15. Studies showed heterozygous mutation increase cancer occurrence as well [52].

It is estimated that the prevalence of Nijmegen syndrome is in approximately 100,000 newborns although the exact data is still unknown [53]. Most individuals with NS have West Slavic origins and the largest number of them live in Poland. In the clinical presentation and laboratory diagnostic testing, Nijmegen syndrome and Fanconi anemia show biological overlap. A positive result of chromosomal breakage induced with clastogens such as MMC and DEB can be seen both in Fanconi anemia and Nijmegen syndrome. Translocations or inversions between chromosomes 7 and 14 can be seen its feature in Nijmegen syndrome [54].

The genetic cause of NS is due to the mutation of NBN gene mutation with homozygous c.657_661del5 on chromosome 8q21.3, resulting in nibrin protein dysfunction which is involved in several critical cellular functions, including the repair of damaged DNA to maintain the stability of the genomic function when breaks of DNA strands happen in the stage where the genetic material in chromosomes exchanges for cell division. As a result, affected individuals are sensitive to radiation and other agent exposures [55, 56]. The molecular tests to confirm the diagnosis of a suspected proband are the analysis of exon 6 to determine if the c.657_661 del5 allele and the analysis of entire NBN gene by the sequencing method.

### 3.3 Bloom syndrome

Bloom syndrome (BSyn) is also named as Bloom-Torre-Machacek syndrome and Bloom-Torre-Machacek syndrome. BSyn is an autosomal recessive pattern characterized with short stature, learning disability, a skin rash, sensitive to sun exposure, serious medical complications such as mild immune-deficiency, chronic obstructive pulmonary disease, varying degree of infertility in both male and female, increased risk of diabetes. Increased risk of cancers to 5–8-folds in earlier life, commonly seen myelodysplasia, leukemia, lymphoma, adenocarcinoma and other types of cancers in epithelial tissues are the characteristics of BSyn as well [57]. Cytogenetics findings are the aberrant chromosomal rearrangements including quadriradial, chromatid gaps and breaks, increased frequency of SCE from the cultured lymphocytes [58].

Molecular studies demonstrated that mutation of BLM gene which is a 4528-bp cDNA sequence defines BLM containing a long open reading frame encoding a 1417-amino acid protein with 22 exons and is located on chromosome 15q26.1 resulted in RecQ helicase dysfunction in BLM protein is the cause of this disease. The BLM protein helps to maintain genome stability and integrity as the caretakers of the genome and also prevents the excess sister chromatid exchanges [59–62]. As a result, SCE is increased to 10-folds under the condition BLM gene mutated. In addition, chromosomal breakage is increased in individuals with Bloom syndrome [63–66].

### 3.4 Ataxia telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive inherited disorder first described in 1926 by two French physicians, Syllaba and Henner [67]. AT is also known as Boder-Sedgwick syndrome or Louis–Bar syndrome and its characteristics including a progressive loss of muscular coordination (ataxia), small cerebellum observed by MRI, increased alpha-fetal protein level and dilated blood vessels in the skin (telangiectasia) caused by a defect in ATM gene. AT affected 1 in 40,000 to 100,000 people worldwide [68] and also affects the nervous, immune and other body systems [69]. The ATM gene provides instructions for making the phosphatidylinositol 3-kinase protein to help control cell division in the normal development and DNA repair [70–72]. Studies demonstrated that increased cancer risk including T-cell leukemia, B-cell type of lymphoma usually, other types of cancers such as ovarian, breast, gastric cancers, melanoma and sarcoma have been reported [73].

Molecular studies revealed the mutations in the ATM gene with several allelic variants located on chromosome 11q23 are responsible for Ataxia-telangiectasia due to the defects in providing instructions for making the specific protein to help in controlling of cell division, DNA repair and in the normal biological development and function of the body particularly in nervous and immune systems.

### 3.5 Ataxia telangiectasia-like disorder

Ataxia telangiectasia-like disorder (ATLD) is a rare autosomal recessive disorder characterized by progressive cerebellar degeneration that shares many clinical presentations with Ataxia telangiectasia but without immune deficiency and telangiectasia, no cancer case report found. It was first designed in 1999 [74] and molecular studies showed that ATLD is caused by inactivating mutations of genes in either homozygous or compound heterozygous [75]. ATLD is usually diagnosed at young at the age starting to walk lacking of coordination and imbalance [76].

Studies showed that there are two mutated genes responsible for ATLD either in homozygous or compound heterozygous. The first is MER11A gene on chromosome 11q21 (ATLD-1) more than 10 different types of variants and the other one is PCNA gene on chromosome 20p12 [77]. Cells from patients demonstrated increased susceptibility to radiation due to the defect of DNA repair pathway. The ATM and MER11A genes are located on the long arm of chromosome 11closely and the biological function of MERA11 protein is linked to Nbs1 in DNA repair.

## 4. Conclusions

In the past decades, the diagnosis of IBMFS and CIS were limited by the few numbers of cases reported, uneven clinical features and the tests from the laboratory in the slow technologies available at that time.

Thanks to the Human Genome Project, researchers have begun to understand the blueprint of the human genome by learning more about the structures and functions of human genes and proteins. With the application of new technologies for the studies, the concept and practice of genetic disease have been profoundly changing. The next generation sequencing technology has also been remarkably successful in the identification of causes of genetic diseases using whole-genome, whole-exome, and transcriptome sequencing.

The studies on IBMFS and CIS have been offering a lot of opportunities by increasing our understanding of the correlations between phenotype and genotype and such studies have been enlightening the other areas particularly in personalized

medicine. Such advances resulted in an unprecedented boom in medical research and an abundance of discoveries linking genetic variants to an assortment of diseases including various cancers. They also have been impacting the genetic field, integrating genomic medicine to primary healthcare practice, bridging the gap between the basic research and clinical application and revealing the pathological basis of genetic diseases which allows the development of accurate and specific tests for disease diagnosis and the eventual translation of research knowledge to clinical therapies.

There are a lot of challenges facing in such a field. Even up to now not all subtypes of IBMFs and CIS are well documented for the clinical and laboratory diagnostic criteria and guidelines due to the disease heterogeneous complexity of the disease, particularly in the developing counties. The clinical manifestations of such patients are highly variable so delay, misdiagnosis and mistreatment were not uncommon under the condition in which such syndromes were treated, that is, with the normal dosage for radiation/chemotherapy. Clinicians working in the field of IBMFS and CIS require a broad clinical knowledge on genetics, hematological and oncological aspects and the ability to refer such patients for testing as well as an experienced laboratory able to perform the particular testing and to translate the laboratory findings correctly into clinical practice. These are the prerequisites for diagnosis of the IBMFS and CIS as well. So cooperation of Multi-displines including genetics, hematology, endocrinendonology, immunology, microbiology, oncology and surgical in the clinic is required for a team in the diagnosis and treatment and also is required from cellular, protein and molecular levels in the laboratory testing, generally performed in a qualified and experienced laboratory. Diagnosis and differential diagnosis on IBMFS and CIS can be difficult sometimes due to the nature of disease and the lack of the specific techniques. Inherited cancer can be the early presentation of the disease as a reason.

Diagnosis on patients with IBMFS and CIS also is challenging, particularly in its early phase. Mismanagement from the misdiagnosis of IBMFS and CIS was not uncommon in some regions and countries because IBMFS and CIS is a genetically and phenotypically heterogeneous disease and also because IBMFS and CIS share many clinical features with several group diseases/syndromes. In research, the precise biological activities and the roles of the FA proteins remain still undetermined because most FA proteins in the core complex have no enzymatic motif which is an obstacle to understanding their molecular functions.

However, from a diagnostic perspective, we are still expecting the development of the ideal technologies for genetic disease testing with the features of specificity, sensitivity, accuracy, reliability, high throughput capacity, reproducibility, low cost and ease of operation because about 45% of patients with IBMFS and CIS need to be identified genetically. Furthermore, despite our vastly improved knowledge of human genetic variations, studying associations between genetic disease genotype and phenotype still remains a major challenge and there are many of mysteries unknown in the functional genetics causing diseases.

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