Phenotypes and genotypes of the chromosomal instability syndromes

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Abstract: As defined initially, chromosome instability syndromes (CIS) are a group of inherited conditions transmitted in autosomal recessive pattern characterised with both mental and physical development delay generally. They are also with other medical complications in individuals with CIS commonly including different degree of dysmorphics, organs/systems dys-function and high risk of cancer predisposition. Chromosomal breakage from CIS can be seen either in spontaneous breakage around 10–15 % observed in Fanconi anemia or induced by clastogenic agents such as mitomycin (MMC), diepoxybutane (DEB). The spontaneous chromosome breakage is less common but it correlates with patient clinical severity. Relative high rates of some types of CIS can occur in certain ethnic groups. Individuals with CIS are commonly in childhood and these disorders are often lethal. Diagnosis is complicated usually because the symptoms presented from individuals with CIS may be varied and complex. Advances in molecular level have identified genes responsible for such group diseases/disorders demonstrated that CIS are characterized by the genome instability, defect in DNA repair mechanisms. Latest advances in high-throughput technologies have been increasing sequencing capabilities to facilitate more accurate data for such syndrome researches. CIS are the typical rare diseases and becoming more challenges in pediatrics clinic. In the last two decades, there were no many articles to review and analysis CIS together to comparing their phenotypes and genotypes. In this article, the similarity and differences of the phenotypes and genotypes of CIS were reviewed to understanding the whole profiles of CIS to assist laboratory genetic diagnostic services in CIS and for the confirmation from the clinical referrals.

Keywords: Chromosomal instability syndromes (CIS); chromosomal breakage syndromes; genomic instability; cancer predisposition

Introduction

Chromosomal instability syndromes (CIS), are also known as chromosomal breakage syndromes are a group of genetic disorders that are typically transmitted in an autosomal recessive pattern of inheritance defined on the basis of cell culture in vitro that 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. There are several diseases/disorders characterised and classified as chromosomal instability syndromes so far and commonly known as: Fanconi anaemia, Nijmegen breakage syndrome, Bloom syndrome, Ataxia telangiectasia and Ataxia telangiectasia-like disorder (1).

The common cause of chromosomal instability syndromes is the defects of genomic maintenance and DNA repair they are overlapping and sharing some clinical features as summarised in *Table 1*.

Studies on CIS for better therapies have achieved exciting successes not only beneficial to CIS self but also beneficial to other diseases. One of the CIS, Fanconi anemia

Table 1 Phenotypes and genotypes of chromosomal instability syndromes

Syndromes	Phenotypes	Locations on chromosomes	Mutant genes	Protein functions	Cancer predisposition
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 and T	Various	Yes
Nijmegen breakage syndrome	Microcephaly and mental retardation, immunodeficiency, radiation sensitivity	8q21.3	Nbs1	BRCT-containing protein	Yes
Bloom's syndrome	Immunodeficiency, premature aging	15q26.1	NLM	DNA helicase	Yes
Ataxia telangiectasia	Neurodegeneration, immunodeficiency, premature aging, radiation sensitivity	11q23	ATM	Protein kinase	Yes
Ataxia telangiectasia -like disorder	Cerebellar degeneration, radiation sensitivity	11q21	Mre11	Exonuclease/ end-onuclease	Proposed but no report seen

is the disease achieved a success in stem cell transplantation using umbilical blood in 1988 (2) and as an effective therapy for many different types of diseases most commonly in malignancies in clinical application since then.

In addition, studies on CIS found that majority of them are associated with cancers 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 19 responsible mutated genes and 5 of them are associated with breast cancer (3). It is not surprising that studies on Fanconi anemia as an example in CIS is named as the paradigm in the studies in cancer and aging (4).

Fanconi anemia (FA)

FA is the most common and representative type of chromosomal instability syndromes. FA is usually inherited as an autosomal recessive trait, but it can be an X-linked recessive in the subtype B. Patients with FA are characterised with progressive bone marrow failure which it is named as one type of inherited bone marrow failure syndromes, congenital abnormalities and susceptibility to malignancies, commonly in MDS, AML, and solid tumors, commonly in carcinoma of the oropharynx and skin, head and neck squamous cell carcinoma, liver tumors, vaginal squamous cell carcinoma and brain tumors. Individuals with FA also can suffer one, or more types of cancers (5,6). Cells from FA patients exhibit a hypersensitivity to DNA interstrand cross-linking agents such as mitomycin (MMC)

and diepoxybutane (DEB). 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. Studies showed that chromosome abnormalities with 7 and 3 had a poor prognostic indication value (7).

A total of 19 subtypes/complementation groups have been classified and 19 responsible genes have been identified respectively (3) as summarised in *Table 2*. *FA* genes encoded proteins participate in the DNA repair. Eight (*FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, *FANCL and FANCM*) of the 19 FA proteins formed a FA core complex interacting each other to active the FANCI-FANCD2 protein complex to a monoubiquitinated form to interact with DNA repair proteins (8,9). Five (FANCD1 known as BRCA2 and FANCS known as BRCA1), FANCJ, FANCN and FANCO) of the *19 FA* genes are found to associate with breast cancer (10). These findings made a link between FA and cancer through DNA repair mechanism.

Nijmegen syndrome (NS)

The name of NS derives from the Dutch city Nijmegen where the condition was first described. It also named as Berlin breakage syndrome, Ataxia-Telangiectasia variant 1. It is an autosomal recessive inherited disease with a complex health problematic conditions typically characterised

Table 2 Summary of 19 Fanconi anemia genes identified and locations on chromosomes

Complementation group	Gene's symbol	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

Data extracted from the Rockefeller University—Fanconi Anemia Mutation Database at www.rockefeller.edu/fanconi.

by short stature, microcephaly, distinctive facial feature, recurrent respiratory tract infections, mental development delay from infancy to childhood, dys-functional 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 (11).

Most individuals with NS have West Slavic origins and the largest number of them live in Poland.

It is estimated that the prevalence of Nijmegen Syndrome is in approximately 100,000 newborns although the exact data is still unknown (12).

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 (13).

The genetic cause of NS is due to the mutation of *NBN* gene mutation with homozygous c.657_661del5 on chromosome 8q21.3, resulted in nibrin protein dysfunction which it 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 are happened in the stage of the genetic material in chromosomes exchanged for cell division. As a result, affected individuals are sensitive to radiation and other agent exposures (14,15). 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.

Bloom syndrome (BSyn)

BSyn also named as Bloom-Torre-Machacek syndrome, is a congenital telangiectatic syndrome with the autosomal recessive pattern characterised 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 infertile 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 is the characteristics of BYyn as well (16). Cytogenetics findings are the aberrant chromosomal rearrangements including quadri-radial, chromatid gaps and breaks, increased frequency of sister chromatid exchange (SCE) from the cultured lymphocytes (17).

Molecular studies demonstrated that mutation of *BLM* gene which it is a 4,528-bp cDNA sequence defines BLM containing a long open reading frame encoding a 1,417-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 to prevent the excess sister chromatid exchanges as well (18-21). 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 (22-25).

Ataxia telangiectasia

Ataxia telangiectasia is an autosomal recessive inherited disorder. It was first described in 1926 by two French physicians, Ladislav Syllaba och Kamil Henner (26). It affected 1 in 40,000 to 100,000 people worldwide (27). Ataxia telangiectasia with several complementation groups 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 which it. It also affects the nervous, immune and other body systems (28). The *ATM* gene provides instructions for making the phosphatidylinositol 3-kinase protein to helps control cell division in the normal development and DNA repair (29-31).

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 (32).

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.

Ataxia telangiectasia-like disorder (ATLD)

ATLD is a rare autosomal recessive disorder characterised by progressive cerebellar degeneration that share many clinical presentations with Ataxia telangiectasia but without immune deficiency and telangiectasia, no cancer case report found. It was first designed in 1999 (33) and molecular studies showed that ATLD is caused by inactivating mutations of genes in either homozygous or compound heterozygous (34). ATLD is usually diagnosed at young at the age starting to walk lacking of coordination and imbalance (35).

Studies showed that there are two mutated genes responsible for ATLD either in homozygous or compound heterozygous have been identified. 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 (33). 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.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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