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# Chromosome instability syndromes

**A. Malcolm R. Taylor**[1,*], **Cynthia Rothblum-Oviatt**[2], **Nathan A. Ellis**[3], **Ian D. Hickson**[4], **Stefan Meyer**[5,6], **Thomas O. Crawford**[7], **Agata Smogorzewska**[8], **Barbara Pietrucha**[9], **Corry Weemaes**[10], **Grant Stewart**[1]

[1]Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, UK

[2]AT Children's Project, Coconut Creek, FL, USA

[3]The University of Arizona Cancer Center, Tucson, AZ, USA

[4]Center for Chromosome Stability, Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark

[5]Stem Cell and Leukaemia Proteomics Laboratory, and Paediatric and Adolescent Oncology, Institute of Cancer Sciences, University of Manchester, Manchester, UK

[6]Department of Paediatric and Adolescent Haematology and oncology , Royal Manchester Children's Hospital and The Christie NHS Trust.

[7]Department of Neurology and Pediatrics, Johns Hopkins University, Baltimore, MD, USA

[8]Laboratory of Genome Maintenance, Rockefeller University, New York, NY, USA

[9]Department of Immunology, The Children's Memorial Health Institute, Warsaw, Poland

[10]Department of Pediatrics (Pediatric Immunology) Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, Netherlands

## Abstract

Fanconi anaemia (FA), ataxia telangiectasia (A-T), Nijmegen breakage syndrome (NBS) and Bloom syndrome (BS), are clinically distinct, chromosome instability (or breakage) disorders. Each disorder has its own pattern of chromosome damage, with cells sensitive to particular drugs that indicate a likely different underlying defect in each case. In addition, each syndrome shows a predisposition to cancer. Understanding the molecular and genetic basis of these disorders has revealed mechanisms of recognition and repair of DNA double strand breaks, DNA interstrand crosslinks and DNA repair during DNA replication. Specialist clinics for each disorder have provided the concentration of expertise needed to tackle their characteristic clinical problems and improve outcomes. While some treatments of the consequences of a disorder may be

* a.m.r.taylor@bham.ac.uk .

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possible, for example hematopoietic stem cell transplantation in FA and NBS, future early intervention to prevent complications of disease will depend on a greater understanding of the roles of the affected DNA repair pathways in development. An important realisation has been the predisposition to cancer in carriers of some of these gene mutations.

## Introduction

The chromosome instability syndromes Fanconi anaemia (FA), ataxia telangiectasia (A-T), Nijmegen breakage syndrome (NBS) and Bloom syndrome (BS) are a group of predominantly recessively inherited conditions associated with defects in DNA repair mechanisms, leading to chromosomal instability, chromosomal breakage and an array of phenotypic consequences, including an increased tendency to develop malignancies. Each condition has distinct molecular features. In FA, mutations in any of the 22 *FANC* genes (but most commonly *FANCA*, *FANCC* and *FANCG*[1–5] affect the repair of DNA interstrand crosslinks (ICLs) — a component of which is homology directed repair (Figure 1). In A-T and NBS, mutations in *ATM* and *NBN*, respectively, affect the resolution of DNA double strand breaks (DSBs) (Figure 2). In BS, mutations in *BLM* (encoding Bloom syndrome protein)[6] affects several aspects of homologous recombination pathways, including DNA stability of replication forks during unperturbed and perturbed DNA replication, DNA end resection (Figure 3) and the dissolution of double Holliday junctions (Figure 4), leading to the presence of chromatid interchanges (quadriradials) and highly elevated levels of sister chromatid exchanges (SCEs). Mutations in TOP3A (encoding topoisomerase 3α), RMI1 and RMI2 (encoding the RecQ-mediated genome instability proteins) have been reported recently as conferring a BS-like disorder (BSLD), featuring small body size and, in those with TOP3A and RMI2 mutations, some dermal abnormalities. A-T-like disorder (ATLD) is caused by mutations of MRE11 (encoding DSB repair protein MRE11). A single case of NBS-like disorder (NBSLD) caused by mutation of RAD50 (encoding DNA repair protein RAD50) has been reported, with increased radiosensitivity. The mutations in these ‘related’ disorders affect components of the same protein complexes as in the respective disorders. We might expect the number of these related disorders to increase in the coming years as new genetic disorders are recognized.

At the clinical level, all these syndromes share a predisposition to cancer but with each having its own spectrum of tumours. The greatest phenotypic heterogeneity is observed in FA and A-T, with the populations of patients with NBS and BS each being more homogeneous. FA is commonly diagnosed in childhood in individuals with variable but distinct patterns of congenital or developmental abnormalities including short stature, microcephaly and café au lait spots and malformations affecting the thumbs or radial ray. Bone marrow failure (BMF) and predisposition in particular to acute myeloid leukaemia (AML) and squamous cell carcinoma (SCC) of the aero-digestive system are characteristic features. Cells from patients with FA display chromosomal breakage and cellular hypersensitivity to ICL-inducing agents (such as diepoxybutane, mitomycin C and cisplatin, a characteristic that is used as a diagnostic test for FA[7]; importantly some FA patients also show increased radiosensitivity.

A-T is a progressive neurodegenerative disease, with onset in early childhood. Characterized by increased radiosensitivity at the cellular level (in which cultured cells are unusually sensitive to the effects of ionizing radiation (for example, by reduced cell survival or increased chromosome damage) and at the clinical level (whereby careful consideration is required before exposing patients to radiotherapy or radiomimetic cytotoxic drugs), A-T also shows typical chromosome translocations in T cells (mainly involving chromosomes 7 and 14) and predisposition to lymphoid tumours in childhood. Patients with A-T show an increased risk of carcinoma including GI tract tumours, endocrine tumours and female breast cancer in adulthood[8,9] (including one male breast cancer[9]). Ataxia telangiectasia-like disorder (ATLD) is clinically very similar to A-T and is caused by specific mutations of *MRE11*.

NBS is another radiosensitivity disorder that was first described in two Dutch brothers from a consanguineous family[10] with microcephaly, growth deficiency, learning difficulty, immunodeficiency and chromosomal rearrangements (resembling those in A-T). Patients with NBS have craniofacial features that include receding forehead, prominent mid-face with long nose and philtrum, receding mandible, epicanthic folds, sparse hair, large ears and subtle sclera telangiectasia. Some have learning difficulty, and congenital malformations include brain malformation, clinodactyly, syndactyly, anal atresia, hydronephrosis, hip dysplasia and ovarian failure. Skin abnormalities common in NBS include café au lait spots, vitiligo spots, sun sensitivity of eyelids, pigment deposits in eye fundus, cutaneous telangiectasias and skin and organ granulomas. NBS predisposes mainly to lymphoid malignancies. A single case of Nijmegen breakage syndrome-like disorder (NBSLD) caused by mutation of *RAD50* has been reported[11], with increased radiosensitivity.

Patients with BS display proportional small body size, including microcephaly as the most characteristic clinical feature. Small size is frequently accompanied by various other features including a telangiectatic sun-sensitive facial erythema, café au lait spots and other dermal pigmentation abnormalities, a characteristic facial appearance with a high-pitched, squeaky voice, immune system deficiencies with increased infections, reduced fertility, gastrointestinal upsets and feeding problems and endocrine abnormalities. The most common complication of BS is the development of cancer. Cancer develops earlier than normal and many persons with BS have developed multiple cancers. Almost all cancer types are reported to occur in BS, the most common ones being leukemias, lymphomas, colorectal cancers, and breast cancers. An early onset of type II diabetes and chronic obstructive lung disease are also common complications in BS. Mutations in *TOP3A*, *RMI1*, and *RMI2* have been recently reported as conferring a Bloom syndrome-like disorder, featuring small size and in persons with TOP3A and RMI2 mutations some dermal abnormalities. As in BS, these conditions exhibit an increased frequency of SCEs.

In this Primer, we describe our understanding of the genetic and molecular bases of these disorders, including the relationship of the defects to the predisposition to different cancers. We point out examples in which the pathogenesis of some of the presenting clinical features remain unclear and describe improvements in patient care that have an impact on survival and quality of life.

## Epidemiology

### Fanconi anaemia

Causative mutations with an estimated average global carrier frequency of 1/180 have been found, so far, in 22 *FANC* genes. Of these, >80% of mutations occur in *FANCA*, *FANCG* and *FANCC*[1–5] with no sex preference; mutations in *FANCE* and *FANCF* comprise ~8% and *FANCD1* ~3% of *FANC* mutations. FA caused by mutations in the other 16 *FANC* genes is rare, comprising small numbers of cases of each. Although FA is uncommon, the incidence varies owing to founder mutations in specific ethnic groups, such as Askenazi Jews and Spanish Gitanos (gypsies)[12,13]. With improved management the prevalence of FA is rising; data from the northwest of England suggest a current prevalence of 5 per million population[14], which seems to have doubled in the past two decades.

### Ataxia telangiectasia

The prevalence of A-T in the UK is ~3 per million population[15], with an estimated ~200 cases (ascertainment close to 100%); similar proportions are expected in Germany, France and Italy. The estimate for the number of affected individuals in the United States is ~1,000 in a population of ~325 million. Median survival in A-T is 25y with a wide range[16] Individuals of both sexes, all races and ethnicities are equally affected by A-T; however, the prevalence of A-T may be higher in consanguineous populations or those populations with a founder effect. ATLD accounts for ~20 published cases worldwide so far.

### Nijmegen breakage syndrome

Although single patients with NBS are reported from all over the world, the majority of patients with NBS have a restricted geographical origin (Slavic and, in particular, Polish or Czech descent) and carry a common founder mutation, 657del5 in exon 6 of the *NBN* (formerly *NBS1*) gene. The prevalence of the founder mutation in the Czech Republic (1:154), Ukraine (1:182) and Poland (1:190) is high[17]. It was estimated that the founder mutation occurred less than 300 generations ago[18], thus supporting the view that the original mutation predated the historic split and subsequent spread of the “Slavic people”[19]. The founder mutation and other mutations have been found in many countries in Western Europe, North and South America and New Zealand[20,21]. By contrast NBSLD is extremely rare with ~5 patients identified in Europe ever.

### Bloom syndrome

Based on an estimate from the ExAc database, which is a sample of convenience consisting largely of Western European whites, the frequency of disease-causing alleles in *BLM* is 0.00138. Consequently, the expected incidence of BS would be 2 cases for every million live births in this population. As expected from this calculation, BS is a remarkably rare disorder with <300 reported cases worldwide. However, this is likely to be a significant underestimate due to inconsistent recording in many countries. For example, based on the frequency of a founder allele in Slavic peoples, there should be several thousand cases in the Russian Federation yet only a few cases have been reported in the literature. Females are just as likely to be affected as males. However, there is a slight under-diagnosis of

females because expression of the facial erythema is not quite as severe[18]. As with many autosomal recessive disorders, the frequency of consanguinity is higher than expected; the parents of affected individuals are known to be related in approximately one-third of families. In another third of families, the parents are Ashkenazi Jewish, which is discussed below (Diagnosis, screening and prevention). The major cause of death in BS is from cancer. The average lifespan has been reported as 27 years, but this estimate is low because it is weighted by deaths from earlier cohorts and does not yet take into account improvements in cancer treatments[22].

Since the chromosome instability syndromes are associated with large increased risks of cancer it might be predicted that heterozygous normal carriers of these gene mutations might also be at an increased risk of cancer through mechanisms such as loss of heterozygosity (Box1) and hapoinsufficincy.

## Mechanisms/pathophysiology

### Fanconi anaemia

Most of the mutations of any of 22 different *FANC* genes implicated in FA are recessively inherited, with the exception of *FANCB* (which is X-linked) and RAD51/FANCR (which is dominant). A much more severe clinical phenotype is attributed to mutations in genes such as *FANCS* and *FANCD1*. The proteins encoded by *FANC* genes are implicated in a common pathway necessary for the repair of DNA ICLs, lesions that covalently link two strands of DNA and block both replication and transcription. Unrepaired or misrepaired ICLs lead to stem cell failure (and in turn to developmental abnormalities and bone marrow failure) and genomic instability (leading to cancer).

The Fanconi repair pathway is activated during DNA replication whereby Fanconi proteins (Box 2) are recruited to the ICL-stalled replisome. FANCL[23], an E3 ubiquitin ligase in a multisubunit protein complex known as the core complex (consisting of FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM and FANCT (also known as UBE2T)), mono-ubiquitylates FANCI and FANCD2, which stably localize to the lesion[24,25]. Once ubiquitylated, FANCI and FANCD2 recruit effectors that are responsible for cleaving the DNA, a step performed by the nuclease FANCQ (also known as XPF) in association with FANCP (also known as SLX4)[26,27], and a DNA synthesis step that is performed by a translesion polymerase FANCV (also known as REV7)[1]. Once the lesion is excised and partially repaired, proteins necessary for homology-directed repair (FANCD1, FANCR (also known as RAD51), FANCS, FANCJ (also known as BRIP1), FANCN (also known as PALB2), FANCO (also known as RAD51C), FANCU (also known as XRCC2)) complete the repair[28,29]. This last step is regulated by another E3 ubiquitin ligase in the pathway, FANCW (also known as RFWD3)[3,30,31].

Although responses to DNA ICLs have been best studied, the Fanconi proteins are also activated as a result of a plethora of other problems that occur during DNA replication. Their function has been identified at common fragile sites, which represent difficult to replicate regions[32] and at sites of collisions between replication and transcription machinery, in which they are implicated in the clearance of R-loops (a three-stranded nucleic acid structure,

composed of a DNA:RNA hybrid, that forms during transcription)[33,34]. Finally, Fanconi proteins including the BRCA proteins, are also involved in protection of stalled replication forks against degradation by DNA nucleases[35–37]. It remains to be determined if the non-ICL repair functions of the majority of Fanconi proteins contribute to the phenotypes of patients with FA. It is likely, however; that the defect in global homology directed repair in patients with biallelic mutations in BRCA2/FANCD1 and PALB2/FANCN explains the very severe disease characterized by early onset AML and embryonal tumours including medullobastoma in these patients[28,38–40].

The pathophysiology of haemopoietic stem cell (HSC) failure and acceleration of tumorigenesis in FA continues to be under investigation. It is clear that FA-deficient HSCs have an autonomous DNA repair defect. Damaged HSCs die due to the activation of p53 and p21-dependent apoptosis[41] resulting in a progressive decrease of bone marrow cellularity necessitating HSC transplantation in FA patients. The key question in the field is what the source is of DNA damage. Mere re-entry of HSCs from quiescence into the cell cycle results in DNA damage that precipitates bone marrow failure if the Fanconi pathway is deficient in the mouse[42]. This finding would imply that lesions encountered during replication are to be blamed. A strong case is being built that such lesions would come from endogenous metabolites in the form of reactive aldehydes, including acetaldehyde and formaldehyde[43–45]. Consistent with data from mouse studies patients with FA with concomitant inherited deficiency of *ALDH2*, the enzyme that metabolizes acetaldehyde and is responsible for preventing alcohol-induced flushing, have increased number of developmental abnormalities, earlier onset of bone marrow failure and leukaemia[43].

### Ataxia telangiectasia and Nijmegen breakage syndrome

Despite similarities between the cellular defects displayed by cells derived from patients with underlying DNA repair deficiencies, the impact that this has on the development and maintenance of specific tissues/organs can be strikingly different, particularly with respect to the nervous system. Broadly speaking, DNA repair deficiencies either give rise to microcephaly or progressive cerebellar degeneration. The underlying reason for this stark contrast in disease-associated neuropathology and how it is related to specific repair deficiencies is not well understood. This is exemplified by the related chromosome instability disorders A-T and NBS, which exhibit overlapping clinical and cellular phenotypes but one is associated with neurodegeneration and the other abnormal neurodevelopment. For this reason, how particular DNA repair deficiencies contribute to the different neuropathologies exhibited by patients with A-T, NBS and other related genome instability disorders, will be discussed together to allow specific comparisons to be made. However, it should be noted that whilst both A-T and NBS are considered as related disorders, often the overlapping clinical and cellular phenotypes e.g. immunodeficiency or radiosensitivity, do differ in severity.

The protein kinase ATM (Box 2), in conjunction with the related protein kinases DNA-PK and ATR, are master regulators of the phosphorylation-dependent cellular response to DNA damage. Over 700 potential substrates of ATM[46] have been identified, which has advanced our understanding of the role of ATM in regulating DNA DSB repair, cell

cycle checkpoint activation and DNA damage-induced apoptotic pathways[47]. Furthermore, patients with A-T, ATLD, NBS, NBSLD (and RIDDLE syndrome caused by mutations in *RNF168*) all display a cellular hypersensitivity to ionising radiation (with A-T being the most radiosensitive by cell survival), and in A-T and NBS a clinical radiosensitivity. They also often display immunodeficiency, problems with fertility and an increased predisposition to lymphoid tumours. Given the role of physiologically-induced DSBs in promoting meiotic recombination and somatic recombination in the adaptive immune system, and that a failure to repair DSBs generated during the latter process is known to facilitate lymphoid tumourigenesis, some aspects of the clinical phenotype of these diseases align well with the underlying cellular DNA repair defect.

How ATM loss contributes to the major neurological features of A-T, that is progressive cerebellar degeneration, remains unclear. The prevailing dogma in the field is that specific neuronal cells within the cerebellum (primarily Purkinje and granule cells) are particularly sensitive to the loss of ATM. One hypothesis is that accumulated unrepaired DNA double strand breaks over time contribute to characteristic cerebellar pathology affecting these cells. However, from the study of other human disorders caused by inherited mutations in DSB repair genes, a DSB repair defect does not commonly give rise to cerebellar degeneration (Figure 2). The exception to this trend is ATLD[48], whose gene product makes up the enzymatic component of the highly conserved MRE11-RAD50-NBN (MRN) DSB repair complex. The involvement of the MRN complex required to efficiently activate ATM following the induction of DNA breaks and that participates in many ATM-regulated DNA damage response (DDR) pathways[47] has strengthened the idea that defective DSB repair may represent the underlying cause of the progressive neuronal decline in patients lacking ATM.

In contrast, hypomorphic mutations in *NBN* and *RAD50* give rise NBS (Box 2) and NBSLD, respectively, which are characterised by the presence of microcephaly but not cerebellar degeneration[11,49–51], therefore, arguing against the hypothesis that an underlying DSB repair defect per se is responsible for the neurodegeneration associated with A-T. Notably, a few patients with *MRE11* mutations have also been identified that exhibit microcephaly and not cerebellar ataxia, indicating that hypomorphic loss of MRE11 and destabilisation of the entire MRN complex does not necessarily predispose to neurodegeneration[52]. Whilst the mechanism governing whether *MRE11* mutations give rise to cerebellar ataxia or microcephaly is unclear, it is possible that a certain threshold level of cellular NBN and RAD50 is required to protect against the development of microcephaly but is not sufficient to prevent cerebellar atrophy. Intriguingly, in contrast to the embryonic lethality associated with a complete loss of Nbn, a mouse model in which Nbn is only disrupted in the central nervous system displayed both microcephaly and cerebellar ataxia, which could be reversed by the inactivation of *TP53*[53]. This suggests that the ability of unrepaired DNA damage to activate the p53-dependent apoptotic response may play a role in determining the pathological outcome of a DNA repair deficiency in the developing versus mature brain[54].

Given that the MRN complex and ATM have been implicated in regulating HR-dependent DSB repair, protecting telomeres from inappropriate repair, processing and repairing

programmed DSBs, activating the G1-, intra-S and G2/M-phase DNA damage checkpoints and inducing DNA damage-dependent apoptosis[55], it is difficult to ascribe loss of a particular DDR function of these proteins to a specific clinical deficit. Furthermore, it is known that ATM and the MRN complex also have roles within the cellular response to DNA damage that are independent of each other, for example, facilitating non-homologous DNA end-joining, degrading stalled, unprotected replication forks, the regulation of transcription, mRNA splicing and translation[47,55]. Thus it is conceivable that it is a combination of specific DDR defects including DSB repair that dictates the development of the different neuropathologies observed in A-T, ATLD, NBS and NBSLD. To confuse matters further, mutations in the DNA damage responsive E3 ubiquitin ligase RNF168, which coordinates the ubiquitin-dependent DDR downstream of ATM and the MRN complex[56], have also been identified in a human syndrome exhibiting cerebellar ataxia[57]. However, interestingly, mutations in *RNF168* were originally identified in RIDDLE syndrome, an immunodeficiency syndrome lacking both microcephaly and overt cerebellar degeneration[58].

Defects in other DNA repair pathways not directly linked to DSBs more consistently give rise to cerebellar degeneration rather than microcephaly. Mutations in five factors known to be involved in regulating DNA end processing have been identified in patients who exhibit progressive cerebellar ataxia: *APTX* (mutated in ataxia with oculomotor apraxia, type 1; AOA1)[59], *PNKP* (mutated in AOA4)[60], *XRCC1* (mutated in AOA5)[61], *TDP1* (mutated in spinocerebellar ataxia with axonal neuropathy, type 1; SCAN1)[62] and *TDP2* (mutated in spinocerebellar ataxia autosomal recessive type 23; SCAR23)[63]. Functionally, these factors have been implicated in mediating the repair of reaction intermediates arising from failed topoisomerase 1- (TOP1) and topoisomerase 2 (TOP2)-dependent processes[64–66]. Given the neurological similarities between A-T and these ataxias, and the physiological relevance of abortive topoisomerase lesions, which are likely to arise at relatively high frequency in transcriptionally active cells such as those in the cerebellum, defective signalling and/or repair of these lesions could contribute to the progressive neurodegeneration in these disorders[67–69]. Consistent with this, cells devoid of ATM are hypersensitive to genotoxic agents that inhibit both TOP1 and TOP2. Moreover, ATM has been demonstrated to phosphorylate both TDP1 and PNKP; in the case of TDP1, phosphorylation stabilises the protein and facilitates its binding to XRCC1, whereas phosphorylation of PNKP enhances both its DNA kinase and phosphatase activities and its localisation to DNA breaks[70–72].

In addition to responding to abortive Top1-associated DNA lesions, TDP1, XRCC1 and PNKP in conjunction with APTX have also been implicated in responding to and repairing oxidative DNA damage induced by reactive oxygen species (ROS). Since mitochondria are one of the main intracellular sources of ROS, it is perhaps not surprising that these four proteins in combination with a specific isoform of Top1, Top1-mt, and DNA ligase III, which is thought to play a role in ligating repair intermediates occurring during the repair of oxidative damage, are all localised to the mitochondria[73]. Intriguingly, unlike ATR and DNA-PK, the ATM protein is not just localised within the nucleus but is also present, to varying degrees, in a number of cytoplasmic organelles, for example, peroxisomes and the mitochondria[74]. Moreover, it has been demonstrated that ROS can directly activate the kinase activity of ATM, independently of the MRN complex, involving oxidation of the Cys-2991 residue, located just C-terminal to its kinase domain[75]. Whilst

the functional relevance of ROS-dependent activation of ATM and its relationship to the neurodegeneration characteristic of A-T are not fully understood, it likely that this allows ATM to react to oxidative DNA damage that lacks a DNA end (i.e. a DSB) in both the nucleus and mitochondria and to trigger an appropriate anti-oxidative stress response, potentially in part by phosphorylating the repair proteins APTX and PNKP. In keeping with a ROS-dependent function of ATM being important for maintaining cellular homeostasis, it has been known for a long time that A-T cells exhibit elevated levels of oxidative stress, structural and functional mitochondrial abnormalities, dysfunctional mitophagy and an inability to properly repair mitochondrial DNA damage[76 77].

Cerebellar degeneration is also caused by mutations in the *SETX* gene (mutated in AOA2), which encodes an RNA/DNA-directed DNA helicase[78]. Several studies have demonstrated that SETX is involved in resolving R-loops that occur at sites of transcriptional pausing or termination, collisions between the transcription and replication machinery and DNA DSBs localised in transcriptionally active genes[79–81]. However, loss of the function of SETX is unlikely to contribute significantly to the cerebellar pathology in AOA2 via collisions between transcription and replication machinery, because all neurons in the developed brain are post-mitotic. This is consistent with an inability to detect increased R-loop formation and chromosome breakage in the brains of Setx knockout mice, contrasting the situation in the testes of these mice[82,83]. Although, it should be noted that, in a manner similar to mouse knockout models of other human syndromes associated with cerebellar ataxia, Setx deficient mice did not exhibit any cerebellar abnormalities or ataxia[82,83]. However, its role in removing R-loops links well with the functions of APTX, PNKP, XRCC1, TDP1 and TDP2, in terms of repairing DNA breaks from oxidative DNA damage or the failed removal of torsional stress by TOP1 and TOP2 during active transcription. Based on this, it is tempting to speculate that any pathogenetic process that interferes with transcription or increases oxidative stress leads to the progressive degeneration of cells within the brain and nervous system. However, in reality it is unlikely to be this simple. Furthermore, if transcriptional abnormalities are a common link underlying all neurodegenerative processes, then it would seem more likely that specific types of neurodegeneration are caused by specific types of transcriptional abnormalities in specific neuronally-associated genes e.g. the presence/absence of R-loops, whether gene transcription initiation/elongation requires TOP2-dependent DSB induction, the chromatin context of the affected gene i.e. presence/absence of cohesin/CTCF[84–87]. In this respect, it has been suggested that the cerebellar degeneration-associated with loss of SETX may arise due to aberrant termination and splicing of specific genes important for neuronal maintenance[88].

The question of why Purkinje cells in A-T are particularly sensitive to the loss of ATM remains a mystery. The high metabolic and transcriptional activity of neurons coupled with their inability to proliferate means that they are highly dependent on intrinsic protective mechanisms such as anti-oxidants and DDR pathways to maintain the integrity of both their nuclear and mitochondrial genomes. However, whilst this helps to explain why cells within the nervous system are more severely affected when DDR is compromised, this does not explain why Purkinje cells are targeted over other neurons. ATM has been linked to many of the cytoplasmic cellular processes and pathways[89,90] described in ≥40 hereditary spinocerebellar ataxias (SCAs), which superficially share aspects of their neuropathology

with A-T (reviewed in[91]). There are also examples of SCA gene products having direct roles in regulating homologous recombination-dependent DNA repair[92]. Taken together, whilst the cytoplasmic functions of ATM are likely to be important for neuroprotection, it is difficult to completely separate these from the role of ATM in regulating the nuclear DDR following either enzymatically-induced DNA breaks or those occurring through indirect mechanisms (for example, the production of highly reactive metabolic intermediates).

## Bloom syndrome

BLM (Box 2) associates with TOPIIIα, RMI1 and RMI2 in the BTRR complex[93]. Acting in concert, these proteins promote the dissolution of a key intermediate in homologous recombination, the double Holliday junction[94]. This function ensures that certain recombination intermediates are processed without crossing over between the recombining molecules, which is one hypothesis for how BLM serves to limit the frequency of SCEs, which are increased as the hallmark cellular feature of BS[95]. Consistent with these proteins engaging in functional interactions, hypomorphic mutations in *TOP3A* and *RMI1* have been shown to give rise to a BS-like disorder associated with microcephalic dwarfism[96]. As well as processing recombination intermediates, BLM also acts as a general anti-recombinase through its ability to dissociate recombination intermediates, a function that would similarly serve to suppress SCEs[97]. BLM also has a role in promoting the initiation of recombination through an ability to catalyze exonucleolytic resection of the ends of DSBs in association with the DNA2 nuclease[98]; this process creates single stranded DNA onto which the key activator of recombination, RAD51, is loaded. This function might also explain why BLM binds directly to RAD51, which it does in a SUMOylation-dependent manner[99]. In cells lacking telomerase, BLM has also been implicated in promoting the recombination-dependent alternative lengthening of telomeres (ALT) telomerase mechanism, which functions to maintain telomere integrity[100]. The binding of BLM to telomeric repeat-binding factor 2 (TRF2) at the telomere might be relevant to this function. Several connections also exist between the BTRR complex and the Fanconi pathway, including interactions with FANCM, FANCJ and the Fanconi core complex[101–103].

Although cells derived from patients with BS have been used to study BLM function, *BLM* has now been inactivated in numerous human cell lines and in several model organisms. BLM-deficient cells universally show chromosomal instability with excessive chromosome breaks, and exchanges between sister chromatids and homologs, as well as a reduced ability to accurately segregate sister chromatids during mitosis[104]. Over 80 different mutations in *BLM* have been shown to give rise to BS, and these mutations either cause premature protein translation termination or affect highly conserved amino acids in the helicase and associated protein domains[6]. The gene is essential for embryonic development in the mouse, but hypomorphic alleles of mouse *BLM* have been generated, which confer some BS-like features[104]. DNA replication abnormalities are a consistent feature of BLM-deficient cells, including a reduced rate of maturation of replication intermediates. Following replication fork blockade using inhibitory drugs, BLM is required for replication fork stability, protecting against irreversible fork collapse. Excessive fork collapse in BS cells is associated with an increased rate of initiation of new replication forks (new origin firing), which

increases the density of replication forks in both unperturbed cells and cells exposed to DNA damaging agents or replication inhibitors[105]. BLM might also be important for the disruption of certain DNA secondary structures, such as G-quadruplexes, that can impede fork progression. This activity might have a direct role in telomere maintenance through facilitating leading strand DNA synthesis[106,107].

BLM also has a role in mitotic chromosome segregation. During anaphase, most human cells display threads of DNA called ultra-fine DNA bridges (UFBs) that cannot be stained with DNA dyes. BTRR binds to UFBs alongside the PICH translocase[108]. The hierarchical binding of these proteins to UFB DNA was modeled using optical tweezers. This showed how PICH recruits BTRR to bridge DNA, exemplifying how partner proteins can influence the properties of the BTRR complex[109]. It is likely that BLM's association with UFBs is for the purpose of decatenating inter-linked replication or recombination intermediates that have persisted into mitosis. The small size in BS is most likely the result of the increased incidence of replication stress and the overall higher frequency of chromosomal mutations. This leads to a slower proliferation rate of cells and a higher rate of apoptosis, especially during embryonic and fetal development and in tissues where rapid cellular division is required, such as in the development of the immune system. The high frequency of cancer in BS, being its main complication, is most likely the result a 4-fold higher rate of mutation coupled with a 50-fold higher rate of loss of heterozygosity from inter-homolog recombination[110].

## Diagnosis, screening and prevention

Given the rarity of these disorders and their inherent clinical complexity, diagnosis and management can be challenging in underdeveloped or developing parts of the world. The clinical features of all the chromosome instability disorders are quite distinct often enabling a highly probable diagnosis based on clinical signs, symptoms and routine laboratory testing. Desired diagnostic certainty can be achieved with genetic testing. Prevention is not possible, although prenatal diagnosis is available for families with an affected child.

## Fanconi anaemia

**Presentation.—**The clinical suspicion of FA arises in childhood in individuals with variable but distinct patterns of congenital or developmental abnormalities[111] (Figure 5). The most common presenting symptoms are haematological abnormalities in children and young people, including cytopenias (which can affect any lineage), bone marrow hypoplasia or failure, myelodysplasia or AML with complex cytogenetic changes (characteristically involving gains of the chromosomal segment 3q)[112] (Figure 6). Severe phenotypes of FA can also present in the neonatal period with a combination of vertebral anomalies, anal atresia, cardiac malformations, tracheo-oesophageal fistula with oesophageal atresia, structural renal and limb (VACTER-L) spectrum of abnormalities[4,14]. An uncommon but important group of patients can present with early childhood tumours, and FA should be considered if affected children have congenital abnormalities with severe toxicity from cytotoxic treatment. These patients can be affected by mutations in *FANC* genes associated with familial cancer, such as *FANCD1* and *FANCN*[14,40]. At the other end of the spectrum, FA should also be considered in the differential diagnosis of aplastic anaemia, myelodysplasia, AML or early

squamous cell carcinoma (SCC) in younger individuals and also when physical findings are not obvious, as the phenotype can be variable. Manifestations of FA can be very subtle, but may still be associated with severe side effects when treated with cytotoxics[113]. Most males with FA are infertile, and although several women with FA have had children, most are sub-fertile and go through menopause early[114].

**Diagnosis.—**FA is often diagnosed on the basis of bone marrow failure, even when other clinical findings have received prior medical attention. The diagnosis is confirmed by demonstration of the characteristic cellular cross linker sensitivity upon exposure to mitomycin C (MMC) or diepoxybutane (DEB). Ambiguous results obtained with peripheral blood lymphocytes can be caused by genetic mosaicism, and need confirmation using fibroblasts[115]. The detailed genetic diagnosis is determined using exon and panel approaches on next-generation sequencing platforms[116]. Once confirmed, the individual phenotypic manifestations should be assessed in detail, and include a bone marrow aspirate with cytogenetic analysis, including FISH for chromosomal gains of 3q and loss of chromosome 7[112]. For other clinical manifestations, which can involve every organ system, functional assessment and imaging of the central nervous system (CNS), kidneys, heart, ears and hearing, eyes and vision, is carried out, and includes detailed endocrine investigations, as hypothyroidism, in particular, is common in those with FA[114,117–119]. Therefore, a workup of suspected FA should include an abdominal ultrasound and a hearing test and routine biochemistry workup including thyroid function test.

The detailed genetic information can be used for antenatal diagnosis and family screening for mutations in familial cancer-associated *FANC* genes. Siblings should always be screened, even in the absence of clinical findings, as the clinical manifestations can be variable even between those with the same mutations[4].

## Ataxia telangiectasia

**Presentation.—**A-T is complex and substantial variability exists in the severity and appearance of different features[120]. We use the designations of “classic” and “mild” A-T to distinguish ends of the clinical spectrum. In the classic, or more severe, form of the disease (also known as typical, early onset or childhood onset A-T), ataxia first becomes apparent as children start to sit and walk, and an initial wobbly gait fails to improve. Children also have problems standing or sitting still and may sway slowly side-to-side or backwards. In childhood, ataxia progresses with requirement for wheelchair mobility typically beginning in the second decade of life. Eye movement abnormalities emerge in early school years. Dysarthria of speech can occur at any time and may or may not progress. Swallowing difficulties typically worsen in late school and early teen years. Involuntary movements can occur at any age. An important early manifestation may be the increased tendency for sino-pulmonary infections due to variable immunodeficiency and increasing difficulty with swallowing. Cancer and pulmonary disease are the two major causes of death by early adulthood[121]. An increasing number of individuals manifest a less severe form of A-T (also known as mild, variant, atypical, late onset or adult onset A-T). Those with mild A-T present with less severe features or later onset manifestations and generally have longer survival.[122–125] .

Early in life, patients with A-T often manifest features of variable immunodeficiency with associated laboratory features[126]. They may also experience poor growth, delayed pubertal development with gonadal dysgenesis and early menopause. As the patients age, they may experience neuropathy, glucose intolerance and insulin-resistant diabetes, elevated cholesterol and triglycerides, non-alcoholic steatosis and cirrhosis, elevated serum transaminases, low vitamin D levels and osteopenia/osteoporosis[127,128]. Indeed, signs of premature ageing such as graying hair and skin changes may also occur in those with A-T[127].

The paradigmatic ocular telangiectasia often appear after onset of neurological symptoms; their absence is a common cause for delayed diagnosis[129] (Figure 3). Other disorders have features that partially overlap with the A-T phenotype, including cerebral palsy, congenital oculo-motor apraxia, Friedreich's ataxia, AOA1, AOA2, ATLD, NBS and SCAN1. These disorders can be distinguished from A-T by the whole of the clinical course, neurological examination and selected laboratory tests. In some cases, genetic or protein assessment is necessary. Genetic analysis, and the absence of ATM protein or function, generally correlates with the A-T phenotype[130,131] . Detection of more cases of mild A-T can be expected with increasing use of whole-exome sequencing.

**Diagnosis and cascade screening.—**A clinical diagnosis of A-T is suggested by combination of characteristic neurological and non-neurological clinical symptoms and laboratory findings. Although, no single laboratory abnormality is invariantly present, individuals with A-T can show an elevated alpha-fetoprotein (AFP) level after 1 year of age, spontaneous and X-ray-induced chromosomal breaks and/or rearrangements in cultured lymphoblastoid cell lines (LCLs), reduced cell survival following irradiation[132], and cerebellar atrophy on imaging that progresses and does not necessarily correlate with clinical phenotype. Immune abnormalities may include low low serum IgA, IgE, IgG and IgG subclasses; lymphopenia (especially affecting T cells) and decreased immune repertoire diversity[126,133,134]. Confirmatory evidence becomes important to those without the full constellation of symptoms. A definitive diagnosis is secured by confirming the absence or deficiency of ATM kinase activity, measured in either a lymphoblastoid cell line made from the patient's blood or in fibroblasts derived from a skin biopsy, the identification of pathological mutations in *ATM*, or a combination of these findings. Elevated serum AFP is evident in ≥95% of patients with A-T, and should be evaluated in any child with unexplained ataxia of stance or gait >1 year of age[20,135].

Pre-natal genetic diagnosis is possible when prospective parents each have identifiable pathogenetic mutations in *ATM*[136,137]. A recent advance has led to frequent pre-symptomatic diagnosis. In combination with exome sequencing, the newborn screening test for severe combined immunodeficiency (SCID) can identify infants born with other disorders, including A-T, that involve a deficiency or absence of T and B lymphocytes[138,139]. Despite the lack of a disease modifying therapy, early diagnosis permits timely genetic counselling and family education as well as aggressive supportive care. Furthermore, cost-effective carrier testing can be performed in families in whom the *ATM* mutations have been identified in an affected child. In situations where the pathogenetic mutations are not known, but a definitive diagnosis of AT has been made, *ATM*-region

haplotype analysis can be used to determine carrier status amongst related family members. Carrier testing in the general population is costly and challenging because of frequent variants of unknown significance in the very large *ATM* gene.

## Nijmegen breakage syndrome

**Presentation.—**A hallmark symptom of NBS is a progressive microcephaly, which is observed from birth onwards, and typical distinctive craniofacial features (Figure 5)[20].The dysmorphic facial features are very similar among all patients and become more obvious with age[21]. Somatic development is delayed, birth weight, length and head circumference (OFC) are typically below normal. Infants show a growth deficit until the age of 2 or 3 years, when some gain in weight and height is observed. The growth spurt in boys is poor, in girls absent[21]. Girls show no pubertal spurt and poor development of secondary sex characteristics, due to ovarian insufficiency[140]. Puberty in boys is initiated spontaneously and progresses normally. Congenital genito-urinary tract anomalies occur. Both the immunodeficiency and the chromosome instability may predispose patients with NBS to tumour development at an early age. By the age of 20 years >40% of patients with NBS develop cancer[141]. The great majority of malignancies are of lymphoid origin; the most frequent is non-Hodgkin lymphoma. Several patients are known to have developed a second malignancy. Solid tumours including rhabdomyosarcoma have less frequently been noted.

Respiratory infections are present in most children. Recurrent pneumonia and bronchitis may result in bronchiectasis, respiratory insufficiency and premature death from respiratory failure. Meningitis, sinusitis and otitis media with draining ears are observed in some children, as are gastrointestinal infections with diarrhoea and urinary tract infections. Opportunistic infections are very rare[20]. Disturbed antibody responses to tetanus, *Haemophilus influenzae* type B, diphtheria, polio and hepatitis B have been reported.

**Diagnosis and cascade screening.—**A clinical diagnosis is suggested by a microcephaly observed from birth onwards. Dysmorphic features become more obvious with age. Low serum levels of IgA, IgG and/or IgG2, lymphopenia, spontaneous and X ray induced chromosomal breaks and/or rearrangements in cultured cells from patients confirm the diagnosis. The characteristic immunodeficiency includes deficits of serum immunoglobulins, the most frequent of which is IgG (62%), followed by low or undetectable levels of IgA (57%). In contrast, IgM concentrations are normal in 61% and elevated in 14% of patients[21]. Deficiency of IgG subclasses (especially IgG2) can be masked in patients with normal concentrations of total IgG[142]. Lymphocyte subpopulations show reduction in absolute numbers of total $CD3^+$ T cells and of $CD4^+$ T cells in most patients. $CD4^+CD45RA^+$ T cells are almost lacking, there is a profound decrease in αβ $CD8^+$ T cells but up to threefold increase in γδ $CD8^+$ T cells. Natural killer cell counts are normal in most patients[143]. The absolute number of $CD19^+CD20^+$ B cells is reduced in most patients[144]. In 2003 two case reports were published. Both boys suffered from medulloblastoma and were treated with craniospinal irradiation. This resulted in severe toxicity and both boys died[145,146].

Cytogenetic aberrations are present in 10–45% of metaphases of phytohaemagglutinin (PHA)-cultured T cells from NBS patients. Most of the rearrangements occur preferentially between chromosomes 7 and 14 and are typically inversions and translocations, with breakpoints at the site of immunoglobulin or T cell receptor genes.[20]. In colony-forming assays, NBS cells are 3–5 times more sensitive to ionising radiation or radiomimetic drugs than normal cells. NBS cells also display radioresistant DNA synthesis[147].

Neonatal screening for severe primary immunodeficiencies began in 2008. Patients with severe combined immunodeficiency (SCID) have absent or reduced T cell numbers and reduced or non-functional B cells, similar to NBS, which can be detected using dried blood spot testing[138]. A patient with NBS detected by newborn screening has been described[148].

## Bloom syndrome

**Presentation.—**Suspicion of a diagnosis of BS is generally based on failure to thrive combined with the observation of other features, including microcephaly, a facial rash, non-facial skin pigmentation abnormalities, repeated chest and ear infections, as well as a lack of normal growth and weight gain (Figure 5). Males show infertility and there is subfertility in females[149]. With a few notable exceptions (prostate cancer and melanoma), virtually all cancer types are reported to occur[150], which distinguishes BS from other chromosome instability disorders. Many of the reported cases are amongst persons of Ashkenazi Jewish ancestry, reflecting a founder mutation present in approximately 1% of that population. The other significant founder mutation occurs in Slavic populations with an allele frequency of approximately 0.4%.

**Diagnosis.—**Small size and a rash on the face are fairly non-specific and frequently lead to misdiagnosis. A path to the correct diagnosis usually requires the expertise of a clinical geneticist. Even in well-resourced settings, the diagnosis can take 3–5 years from birth. Many cases of BS were identified from general categories such as idiopathic intrauterine growth deficiency, primordial dwarfism, and failure to thrive. Some cases have been misdiagnosed as other rare syndromes; for example, a misdiagnosis of Russell Silver dwarfism is not infrequent. Historically, suspected cases were tested with a cytogenetic assay to determine the frequency of SCEs in peripheral lymphocytes, because until recently this test was pathognomonic for BS. However, elevated SCEs have been identified in cells from individuals with several BS-like disorders caused by hypomorphic mutations in *TOP3A* or *RMI1*. Consequently, direct DNA sequencing of the *BLM* gene is a more definitive test, although in some cases the results can give ambiguous data if the identified variant is not obviously disease-causing. In the case of persons of Ashkenazi Jewish ancestry, the prevalence of the founder $BLM^{Ash}$ mutation makes this analysis more definitive. The rarity of the disorder has largely precluded the development of widespread screening programmes, although $BLM^{Ash}$ mutation analysis within the Ashkenazi Jewish population is now more common. Prevention of conception is practised in a very limited sense, via the pre-nuptual identification of carriers of the $BLM^{Ash}$ mutation in certain orthodox Jewish communities[151]. Prenatal diagnosis is possible with the SCE assay or by *BLM* mutation analysis.

## Management

A common requirement for all these disorders is the need for surveillance for cancer development. Cancer diagnosis can be at any age in FA, A-T and NBS and most frequently in early adulthood in BS. It is important, therefore, that consideration is given, at any age, to the possibility that a tumour is the cause of any unexplained symptoms and that appropriate tests are carried out.

### Fanconi anaemia

Historically, bone marrow failure is the most common and significant manifestation of FA. Platelet counts above 30 $\times 10^9$/L can often be tolerated for years without substantial complications and managed conservatively with watch and wait. The need for intervention arises if bleeding, transfusion dependency or infectious complications evolve. As with other bone marrow failure syndromes, FA-associated hypoplastic haematopoiesis can respond to low dose androgens, which seems to be safe and reasonably tolerated, with many patients maintaining satisfactory blood counts for up to several years[152]. Haematopoietic manifestations of FA and importantly the risk of leukaemic transformation are corrected with haematopoietic stem cell transplantation (HSCT); with the use of T-cell depleted bone marrow grafts and fludarabine-based conditioning, patients undergoing matched family or unrelated transplants have excellent outcomes[153]. HSCT outcome in adults and later stages of disease progression with pre-leukaemic changes and overt leukaemia is also improving[154,155]. When a matched sibling or unrelated donor is available, transplantation can be considered early and elective.

With a growing number of teenagers, young and middle-aged adults with FA, many of whom have had HSCT, non-haematological problems evolve and can become life-limiting[117]. Chronic organ dysfunction as a result of FA itself or HSCT for FA-associated BMF, such as endocrine dysfunction (hypothyroidisms, growth failure, early menopause and infertility) or impaired heart, lung or kidney function, need assessment, monitoring and appropriate management. The most concerning problem for adults with FA is the development of SCCs in the aero-digestive and ano-genital regions[156] (Figure 2), which are difficult to manage as they are often multifocal; due to the patients' inherited cross-linker sensitivity, the treatment can be very toxic[157,158]. Enrolment in a dedicated screening programme with regular detailed inspection of the head and neck and ano-genital region and upper GI endoscopy is important for early effective management, and many centres provide a dedicated service for those patients.

### Ataxia telangiectasia

A-T is a multisystem disease, in which management is symptomatic and supportive. Regarding the neurological symptoms, no therapy can slow degeneration, but in some patients intervention may partially ameliorate symptoms. Drugs that may be prescribed for neurological symptoms include trihexphenidyl (an antimuscarinic), amantadine (an antiparkinsonian), baclofen (an antispastic) and botulinum toxin (a paralytic) and less commonly gabapentin (an anticonvulsant), clonazepam (a tranquilizer and antiseizure medication) and pregabalin (a calcium channel blocker typically used to treat epilepsy)[159].

Vision is typically normal, although reading and other saccade-based visual tasks are difficult. Large print or visual targeting techniques may be helpful[160]. Bracing or surgical correction (e.g. tendon transfer) may improve ankle stability to enable walking or weight bearing. Severe scoliosis requiring surgical intervention is relatively uncommon[161].

All people with A-T should have at least one comprehensive immunologic evaluation to assess the number and type of B and T cells (which should be reassessed if the patient undergoes chemotherapy or is treated for longer than a few weeks with a corticosteroid), to assess levels of serum immunoglobulins (especially IgG, IgM and IgA) and to assess antibody responses to T cell- dependent and T cell-independent vaccines[161]. If antibody function is normal, all routine childhood immunizations should be given, except the measles, mumps, rubella (MMR) vaccine (see below)[162]. The risk:benefit ratio of the MMR vaccine may need to be reassessed if any of those diseases become locally endemic; if that occurs, another strategy would be to use prophylactic gamma globulin until the outbreak is under control. Individuals with normal ability to make antibody should receive an annual influenza vaccine, and additional pneumococcal vaccines at intervals to maintain high levels of anti-pneumococcal antibodies. All household members should also receive the influenza vaccine. People with impaired antibody function should receive standard immunoglobulin replacement therapy. Despite having low T-cell numbers, prophylactic antibiotics to prevent opportunistic infections are generally not necessary unless people are treated with chronic corticosteroids, other T-cell immunosuppressive drugs, or chemotherapy. Immunological tests should be repeated if problems with infections occur or worsen[161,162].

Chronic cutaneous granulomas can be associated with A-T[163,164]. These have been associated with replication incompetent vaccine strain rubella virus detected by PCR[165–167]. Smaller or superficial granulomas can be treated with high-potency topical corticosteroids and/or cyclosporine A whereas more extensive lesions may respond to TNF inhibitors[168], direct injection of steroids into the lesion(s)[169] or combination therapy (for example, topical steroids and IV gamma globulin)[170]. No anti-viral drug has yet been found to be effective.

Chronic lung disease is responsible for approximately one-third of the deaths in A-T and early intervention is crucial for preventing or slowing its development. Pulmonary function tests (PFTs) should be performed in all children with A-T starting at 6 years of age and continued annually[162,171]. Management may include the liberal use of antibiotics and corticosteroids (BOX 3). Recurrent lung infections may involve dysfunctional swallow with aspiration[162]. Some people with A-T can be taught to drink, chew and swallow more safely reducing the risk of aspiration. As the nutritional deficit in some people with A-T may be more severe than previously appreciated[172 173], early nutritional intervention and ongoing nutritional support and education for patients, families and caregivers are crucial. Dieticians can recommend ways to improve nutrition (e.g. use of high calorie foods or food supplements). A gastrostomy tube (G-tube or feeding tube) may be recommended[174 175] if a child cannot eat enough to grow or weight at any age cannot be maintained; if dysphagia with aspiration results in respiratory compromise and/or mealtimes are too long or stressful[176]

Cancer treatment should take place only at specialist oncology centers and after consultation with a clinician who has specific expertise in A-T. Standard cancer therapy regimens need to be modified to minimize or avoid cytotoxicity from radiomimetic drugs. Radiation therapy should be used rarely and only at reduced doses. Cyclophosphamide use must be monitored as it has been associated with a later onset of severe haemorrhage from bladder telangiectasia[177]. Even with therapy modifications, some people with A-T who have late stage cancers will develop chemotherapy toxicities[178]. Bone marrow transplants have been successfully performed for haematopoietic cancers in A-T[179,180] but routine use is not currently recommended.

During the school years, children with A-T will need special attention to the barriers faced in school. Recommended modifications for education are described in BOX 4.

### Nijmegen breakage syndrome

Monitoring of the immune system is important throughout the whole life of a patient with NBS as even patients with normal absolute B lymphocyte counts experience significant humoral deficiencies requiring IVIG therapy, which is used in ~68% of patients[144]. HSCT can correct the hematopoietic defect and underlying immunodeficiency in NBS[181]. Survival is superior when reduced-intensity conditioning (RIC) is used, with patients not experiencing relapse of malignancy (median follow up 6 years) in one retrospective analysi[144]. Umbilical cord blood transplantation is less common but in one study rapid and substantial progress in the development of psychomotor and physical skills occurred in the post-transplant period[182].

The prognosis for patients with NBS and malignancies is still poor. Chemotherapy has to be adapted and radiotherapy omitted. In haematological malignancies, curative treatment is possible, adjusting the intensity of therapy to individual risk factors[183,184]. For example, reducing chemotherapy up to 50% especially when using anthracyclines, methotrexate and alkylating agents, is possible. Epipophyllotoxins (etoposide, teniposide), bleomycin and radiotherapy should be omitted[141]. Dosage-reduction of chemotherapeutic drugs seemed to have no disadvantages and reduced toxic adverse effects but does not prevent second malignancies[185].

### Bloom syndrome

Cancer is the main cause of early death in those with BS, and the predisposition includes the development of multiple cancers and cancer types, including leukaemias, lymphomas and carcinomas[150]. An early onset of the disease is also a prominent feature, with a mean age at cancer diagnosis of ~25 years. The main approach to cancer management is heightened surveillance, supported by lifestyle interventions that can help lessen cancer incidence (including minimization of tobacco use, sun exposure (which can also help address facial rash in BS), and irradiation from medical devices or naturally occurring sources such as radon). Awareness of symptoms of cancer and seeking prompt medical attention is considered to be the first defence.

For lymphomas and carcinomas, surgical resection of early lesions most frequently results in cure. Recommendations for cancer surveillance have been developed based on experience in

other cancer-prone syndromes[150]. Although clinical trials on the efficacy of the surveillance recommendations have yet to be conducted, the successful increase in long-term survival of persons with Li-Fraumeni syndrome through frequent imaging studies offers hope that a similar success can be achieved in BS[186]. The recommended imaging studies in BS include abdominal ultrasonography every 3 months beginning at diagnosis and ending at age 8 years for Wilms tumour; whole body MRI every 1–2 years beginning at age 12–13 for lymphoma; annual colonoscopy and biannual fecal immunochemical test beginning at age 10–12 years for colorectal cancer; annual breast MRI beginning at age 18 years; annual skin examination for skin cancer; HPV vaccine for both boys and girls and annual Pap smears for females after reaching adolescence. When individuals with BS have developed cancer, medical providers should be aware of the risk of therapy-related, secondary malignancies. Standard weight-based chemotherapy regimens have resulted in life-threatening toxicities[150]. Dose reduction of the genotoxic chemotherapeutic agents by at least 50% is essential and usually well tolerated. Radiotherapy should be minimized unless it is the only realistic option for cure, and alkylating agents, such as busulfan and cyclophosphamide, should be avoided. Some chemotherapeutic could be tolerated at full weight-based doses, including kinase inhibitors and steroids[149].

At present no remedy can address growth restriction in BS. Growth hormone therapy has had varying effects on growth; however, the question of whether this increases cancer risk is unresolved[187]. Feeding problems are common in children and infants, and there is a marked reduction in adipose tissue. Feeding intervention has been tried at some centres, but no systematic studies have been conducted. Use of high-calorie diets and anti-reflux medication should be considered. Approximately 20% of individuals with BS have developed type II diabetes. Fasting blood sugar measurements and screening for impaired glucose tolerance with haemoglobin A1c are recommended annually beginning at age 10 years to identify pre-diabetes and initiate standard preventive measures. An annual lipid profile and testing thyroid function should begin at age 10 years.

Individuals with BS often have deficiencies in immunoglobulins and are subject to recurrent infections[150]. Those individuals with recurrent sinusitis, more than one incidence of pneumonia in a 10-year period, multiple episodes of bronchitis, or other opportunistic infections, should consult an immunologist. Defects in humoral immunity can be managed with a preferred weekly subcutaneous injection of immunoglobulin or monthly Intravenous immunoglobulin. Finally, women with BS may have early menopause and may benefit from assisted reproductive technology. No remedy for infertility has been found for men with BS, although there is a single case report of confirmed paternity in a man with BS.

## Quality of Life

Various voluntary patient organisations and support groups in different countries collaborate closely with scientific and medical experts to find effective life improving therapies and provide education and support to families affected by Fanconi anaemia, Ataxia telangiectasia and Nijmegen Breakage Syndrome; the rarest of these groups is supported by the Bloom Syndrome Association.

### Fanconi anaemia

The impact of FA on the quality of life depends on the severity of the phenotype with organ dysfunction, timing and consequences of bone marrow failure and the need for HSCT, and cancer development. As with other chronic and life limiting diseases, the effect on the family can be profound[188]. Individuals affected with FA and individuals with a very mild phenotype can have a nearly normal life until their fourth decade; then sometimes the diagnosis is made when subtle clinical patterns are recognised[113]. Classical cases with bone marrow failure in childhood, radial ray abnormalities and short stature normally improve for a long period following successful haematopoietic reconstitution after HSCT, but in many cases this period can be affected by extreme short stature and disability from limb abnormalities. The dramatically increasing incidence of SCC affecting individuals with FA in the third and fourth decade is having a detrimental effect on quality of life in adult patients with FA, sometimes requiring repeated major and sometimes disfiguring surgery[158], and is often life limiting.

### Ataxia telangiectasia

Children with A-T will experience varying degrees of difficulty with school performance due to impaired fine and gross motor coordination (limiting ability to write and use a computer); dysarthria, delay in speech initiation, lack of facial expression, and delayed response times to visual and verbal cues (limiting ability to communicate); and oculomotor apraxia (limiting ability to read). Mental and physical fatigue are common. Individuals with A-T may be further burdened by the appearance of cognitive impairment, even when the impairment itself is mild or does not exist; however, social awareness is typically normal. This disparity can lead to social isolation and depression. Even with these difficulties, many people with A-T have found ways to overcome these difficulties; especially in the presence of a supportive environment in the school. As survival and quality of life have improved, a small but increasing number of people with A-T have been able to transition to higher education and independent living with support.

### Nijmegen breakage syndrome

Developmental milestones are reached at expected times during the first years of life. Patients with normal intelligence or learning difficulty of variable degree have been reported. Longitudinal follow up studies indicate that small children (pre-school) are mostly within the normal range, but go on to develop IQ deficiency, which ranges from mild to moderate. Most children have a striking psychomotor hyperactivity. At older ages, all patients tested were mildly or moderately delayed. All are capable of good social interactions[21]. So far, there have not been any reports of NBS patients having offspring.

### Bloom syndrome

BS impacts both the affected person and the parents or guardians entrusted with that person’s upbringing and education. For the guardians, there can be an emotional struggle of medical uncertainty until a definitive diagnosis is made, made more difficult by having to deal with the feeding problems and sun sensitivity, as well as a search for the explanation for the small size. After the diagnosis, there is the struggle to understand its impact, to

learn what is known and not known about the syndrome, and to identify and organize the personal and societal resources needed to cope with that diagnosis. For the persons with BS, aside from for the accommodations that need to be made for the sun sensitivity and small size, day-to-day life might not be that different compared to anyone else, except for the extra attention received due to their small size. For most persons with BS, intellectual development is normal, although some have difficulty with subjects that require a high level of abstract thought. As children become adults, they come to know the risks that are attached to their diagnosis, and the likelihood that their lifespan might be foreshortened[189].

## Outlook

### Fanconi anaemia

The past two decades have seen dramatic progress in the understanding of the genetics, molecular biology and disease mechanism in FA, and placed FA research firmly in the context of cancer and aging. Clinically, with wide availability of donors and improved conditioning regimens, HSCT has become a routine treatment modality for haematological manifestations of FA, which is likely to further improve as even higher risk transplantions in adults and using unmatched or haplo-identical donors are now successfully carried out[154,190]. While there is still a lot to learn about the role of the FANC pathway in haematopoietic maintenance, clinically for many patients the haematopoietic defect of FA can be successfully corrected. Also for patients without any suitable donor, results of current gene therapy trials aiming to restore impaired haematopoiesis by correction of patient-derived haematopoietic progenitor cells are promising[191]. This progress has transformed FA to a chronic condition of variable severity affecting an increasing number of adults who are now in their fourth and fifth decades. While efforts in identifying compounds that might affect the cellular FA defect show some promise[192,193], the most pressing clinical problem is the high incidence of epithelial cancers and their management. Detailed understanding of the pathogenesis of SCC in FA will be important for effective prevention and monitoring, and targeted strategies for treatment are urgently needed.

### Ataxia telangiectasia

Whole genome sequencing and epigenetic analyses may help identify modifiers of A-T disease severity and reveal additional genotype-phenotype correlations. Analyses of data from growing patient registries[194,195]will inform natural history, improve disease management and aid therapy development.

Difficulty with coordination, to varying degrees, is experienced by all patients with A-T. However, it is not yet known why the cerebellum is so severely affected in A-T, while other areas of the brain are unaffected. Although small animal models of A-T have failed to accurately recapitulate the human neurological phenotype the neurophenotype of the larger and longer lived porcine model for A-T is currently being studied. Researchers are investigating ways to apply recent breakthroughs in the fields of gene and mutation targeted therapies to A-T.

Risk factors for pulmonary decline need to be identified, and the contribution of inflammation to pulmonary disease in A-T needs further investigation. Optimal protocols for preventing decline in lung function and treating lung disease do not yet exist. MRI lung imaging techniques will help advance the field. Additionally, biomarkers and risk factors for the development of cancer in A-T need to be identified. Less toxic treatment regimens are critically needed. Present attention to symptomatic disease modifying therapies include, low-dose corticosteroids (e.g. dexamethasone[196–198] and betamethasone[199,200], 4-aminopyridine[201 202], cannabinoids (e.g. Cannabidiol oil and Marinol), nicotinamide riboside[203] as well as mutation-targeted[204,205] and non-viral gene therapy approaches.

### Nijmegen breakage syndrome

More knowledge of the immunodeficiency in NBS might provide a better understanding of the development of malignancy, especially lymphomas. NBS patients showed much lower numbers of αβ T cells (both $CD4^+$ as well as $CD8^+$) but normal numbers of γδ T cells. Circulating T cells show signs of a senescent phenotype present from young age, which might explain the T cell immune deficiency[206]. Patients with NBS have a high risk to develop a malignancy. Improvements of survival is possible with haematopoietic stem cell transplantation. Reduced conditioning regimens, similar to those used for patients with Fanconi anemia, are well tolerated. Due to the substantial risk of mixed chimerism patients with NBS may tolerate more intensive conditioning regimens than patients with Fanconi anemia, although this requires further observation (Wolska-Kusnierz 2015). It was demonstrated recently that antisense oligonucleotides could enforce alternative splicing in NBS patient cells, generating a p80-nibrin protein. Injecting the same antisense sequences as morpholinos in humanized NBS mice led to efficient alternative splicing in vivo[207].

### Bloom syndrome

Cancer risk is the most pressing issue for persons living with BS; the development of novel cancer therapies that target the particular cellular vulnerabilities of BS cancers holds the best hope for extending life expectancy. At present, however, there are no therapies that exploit this so-called ‘synthetic lethality’ approach to treatment in the way that PARP inhibitors have been used in BRCA1-deficient and BRCA2-deficient tumours[208]. Identifying treatments without toxicity in BS are needed. Furthermore, the efficacy of new immunotherapy approaches to treat cancer needs to be evaluated in BS. Although BS mouse models exist that could be used to test new therapeutics and biological questions relating to body size, there is an urgent need to develop better human cancer models (such as cultured tumour cell lines and patient-derived xenograft models) in BS. Other novel animal models are also needed to address biological questions where mouse models are less valuable, such as the use of porcine epidermis as a model for human skin.

The idea of gene therapy or correction in BS is often considered by the families affected[189], especially in the age of CRISPR–Cas9 genome editing, but the practical issues surrounding reagent delivery make BS a poor first choice to test new advances in this area. There are also many questions regarding the somatic chimerism of corrected, uncorrected, and genetically damaged cells that need to be addressed.

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**BOX1.**

## Increased cancer risk in heterozygous carriers of 'Chromosome Instability Disorder' gene mutations.

Being a carrier of a gene mutation associated with a chromosome instability disorder may increase the risk of cancer. Several studies have investigated the cancer risk of *FANC* mutation carriers. While individual cases of cancer in *FANC* mutation carriers have been described[209] there is no evidence of a statistically significant increased cancer risk for mutation carriers (i.e. first degree relatives) of the commonly mutated *FANC* genes[210 211]. An increased risk of cancer is presumed in FANC family members that are carriers of the hereditary breast and ovarian cancer associated *FANC* mutations, which include *FANCN* (otherwise known as *PALB2*), *FANCO* (otherwise known as *RAD51C*), *FANCS* (otherwise known as *BRCA1*) and *FANCD1* (otherwise known as *BRCA2*), which is the most commonly mutated gene of this subgroup of FA genes[14]. Also for these FA cases, which typically have a severe phenotype, the family history is not always positive, but the number of cases is small. Germline *FANCD1* variants were also identified in a small but significant subgroup of non-FA childhood malignancies[212] .The role of other FA gene variants in susceptibility to sporadic cancer, in particular SCC continues to be investigated, but any clinical risk contribution of these variants for non-FA cancer is not fully understood[213].

Studies on families with A-T have established that female carriers in these families have a doubling of the relative risk for breast cancer compared with the general population in the UK (and a ~5 fold increase in those <50 years of age)[214]; indeed, carrying an *ATM* mutation is considered a moderate risk factor for breast cancer. Some data suggested that there is a further increased risk of breast cancer in carriers of specific *ATM* mutations, in particular the c.7271T>G;p.Gly2424Val *ATM* missense mutation[215,216]. Some evidence also suggests that these carriers have excess risks of colorectal cancer (RR = 2.54, 95% CI = 1.06 to 6.09) and stomach cancer (RR = 3.39, 95% CI = 0.86 to 13.4). Additional long-term studies on A-T families will further clarify these risks. Recent publications on >10,000 tumours in the general population with germline variants and cancer driver genes using The Cancer Genome Atlas data have highlighted the occurrence of biallelic *ATM* mutations across multiple cancer types[217,218] with a strong association with both prostate and gastric carcinoma and a suggestive association with breast cancer, lung adenocarcinoma and pancreatic adenocarcinoma, in accordance with previous work[219,220].

The NBN657del5 mutation is associated with an elevated risk of cancer in heterozygotes[221]. About a 3-fold increase in breast cancer risk for female NBS heterozygotes has been demonstrated[222]. There is an increase in prostate cancer in men and a predisposition to medulloblastoma in paediatric patients[223 224]. More recently, however, *MRE11*, *RAD50* and *NBN* were also reported as intermediate risk breast cancer susceptibility alleles[225].

Heterozygous Bloom syndrome mutation carriers are apparently asymptomatic, although the incidence of some cancers might be mildly elevated[226]. Confirmation of there being

any association between *BLM* polymorphisms and an increased incidence of cancer will require large genome-wide association or sequencing studies.

**Box 2.**

## The affected proteins.

**FANC**

- FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM, FANCT/UBE2T, together, form the Fanconi anaemia core complex. FANCL is the E3 ubiquitin ligase, and FANCT/UBE2T is an E2 Ubiquitin ligase. If the core complex is inactive, FANCI and FANCD2 are not monoubiquitinated resulting in Fanconi anemia.
- FANCI and FANCD Form a heterodimer (ID2 complex) which is monoubiquitinated by FANCL in the core complex. ID2 localizes to DNA interstrand crosslinks and is thought to recruit pathway effectors.
- FANCP/SLX4 is the protein scaffold for FANCQ/XPF, MUS81, SLX1. It is necessary for ICL repair but also for Holliday junction resolution.
- FANCQ/XPF is a structure-specific nuclease necessary for DNA ICL repair when complexed with FANCP/SLX4 and Nucleotide Excision Repair (NER) independent of FANCP/SLX4 interaction.
- FANCV/REV7 is a component of a translesion synthesis (TLS) polymerases Polζ
- FANCD1/BRCA2, FANCJ/BRIP1, FANCN/PALB2 FANCO/RAD51C, FANCR/RAD51, FANCS/BRCA1, FANCU/XRCC2 and FANCW/RFWD3 are proteins that participate in or regulate homology-directed repair during DNA ICL repair but also in response to many other lesions including DSBs. Multiple components have enzymatic activities including 5’−3’ helicase activity of FANCJ, ATPase activity of RAD51, and E3 ubiquitin ligase of FANCS and FANCW[a]

**ATM**

- Member of the PI-3-kinase-like family of Ser/Thr kinases (PIKKs) also containing ATR and DNA-$PK_{CS}$
- When mutated gives rise to the neurodegenerative, chromosome instability disorder, Ataxia Telangiectasia
- Predominatly localises to the nucleus but is also found in cytoplasmic organelles/vesicles e.g. mitochondria, peroxisomes
- Exists as a inactive dimer that is activated in response to DNA double strand breaks by trans autophosphorylation, which is stimulated by binding to the MRN complex
- Can be activated in response to reactive oxygen species via an MRN-independent mechanism involving the oxidation of Cys-2991

- Phosphorylates >700 different nuclear/cytoplasmic protein substrates involved in regulating DNA repair, replication, cell cycle checkpoint activation, apoptosis, telomere maintenance, transcription, chromatin structure, metabolism, growth factor signaling, RNA splicing, protein synthesis, autophagy and vesicular trafficking.
- Somatically mutated in a number of sporadic lymphoid and epithelial tumours e.g. B-CLL, T-PLL, mantle cell lymphoma

**NBN**

- Non-catalytic subunit of the MRE11/RAD50/NBN complex
- When mutated gives rise to the developmental, chromosome instability disorder, Nijmegen Breakage Syndrome (NBS)
- Contains an N-terminal FHA domain and two BRCT domains that mediate the MRN complex binding to MDC1, TCOF1 and CtIP in a phospho-dependent manner
- Contains a C-terminal motif that is important for binding and activating ATM at the sites of DNA double strand breaks
- Implicated in regulating the nuclear localisation of the MRN complex
- Functions to regulate ATM-dependent DNA damage signaling, DNA double strand break end-resection, DNA damage-induced cell cycle checkpoint activation, DNA damage-induced apoptosis, the replication stress response, ATR activation
- Somatically mutated in some lymphoid/epithelial tumours

**BLM**[227–229]

- Member of the RecQ helicase family
- Translocates along ssDNA in a 3’−5’ direction and mediates dissolution of recombination and late-replication intermediates in conjunction with Topoisomerase IIIα and RMI1/2. Dissolution of double Holliday junctions into non-crossover products are proposed to be the main reason why SCEs arise in the absence of BLM
- Catalytic domain contains the helicase active site and a RecQ C-terminal (RQC) region, which comprises both winged-helix domain (for DNA binding) and a $Zn^{2+}$-binding subdomain (for structural integrity)
- Helicase and RNaseD C-terminal (HRDC) domain are implicated in binding to complex and branched DNA structures
- N-terminal domain mediates protein-protein interactions, and is a target for several post-translational modifications
- BS-associated mutations in *BLM* lead either to protein truncation or a catalytically inactive protein

[a]The phenotypes of patients with mutations in genes coding for the HR proteins are variable with mutations in FANCO, FANCR, FANCS, FANCU leading to no spontaneous bone marrow failure (Fanconi anemia-like phenotype) and mutations in FANCD1 and PALB2 leading to a very severe cancer predisposition phenotype.

**BOX 3.**

### Management of pulmonary symptoms in A-T[162,230]

- Liberal use of antibiotics for
  - persistent and/or prolonged upper and lower respiratory symptoms including those that follow a respiratory illness
  - chronic cough with mucus or cough that does not respond to pulmonary clearance techniques
  - individuals with muco-purulent secretions from the chest or sinuses
- Examination of respiratory secretions (from bronchoscopy or induced sputum) may direct antibody therapy for lung infections and help prevent bronchiectasis
- Prophylactic macrolides, inhaled aminoglycoside and/or fluoroquinolones may help reduce exacerbations in people with low lung function, recurrent pneumonias, or bronchiectasis
- Corticosteroids may be beneficial for people with AT and ILD
- Bronchodilators may be useful for treating restrictive (with a component of obstructive) lung disease in A-T
- Clearance of oral and bronchial secretions (using the manual method or with an acapella device or chest physiotherapy vest) can help limit injury from acute and chronic pulmonary infections
  - Evaluation by a pulmonary specialist is necessary
  - Use of chest physiotherapy requires an adequate cough to remove secretions
  - An acapella device is useful for those with a weak cough or decreased lung reserve
- Inspiratory muscle training (IMT) may improve respiratory strength and quality of life[231]. Low dose chest and sinus CT scans should be performed if symptoms are unresponsive to therapy to rule out bronchiectasis, fibrosis, ILD and tumors

**Notes:**

- A pulmonary evaluation should be performed prior to surgical procedures requiring anesthesia.
- All people with A-T should avoid secondhand smoke exposure and have minimal exposure to other environmental pollutants.
- Adequate nutrition to maintain normal body mass index may help maintain respiratory muscle strength and minimize progression of lung disease.

- Gender differences with regard to lung disease may exist.

**BOX 4.**

### Recommendations for school in patients with AT

As individuals with A-T have neurological problems from an early age (e.g.resulting in abnormal eye movements for reading, hand movements for writing/typing etc) in the absence of any learning difficulty, considerable practical help with schooling is the standard.

- Speech-language pathologists may aid communication skills and help educate others about the need for longer response times for people with A-T; however, traditional speech therapy is rarely helpful
- Early use of computers with word completion software and other technologies are helpful
- As hearing is normal and does not deteriorate, an emphasis should be placed on oral learning (e.g. audiobooks)
- Classroom aides can help with writing, mealtimes, toileting and with transportation throughout the school
- Fatigue is a significant part of life with A-T, therefore the need for rest time, shortened school days, a reduced class schedule, reduced homework and modified tests should be revisited as often as circumstances warrant
- As with all children, social interactions with peers are important and should always be taken into consideration
- Children with A-T often have excellent insight into how best to solve functional problems and their involvement should be encouraged

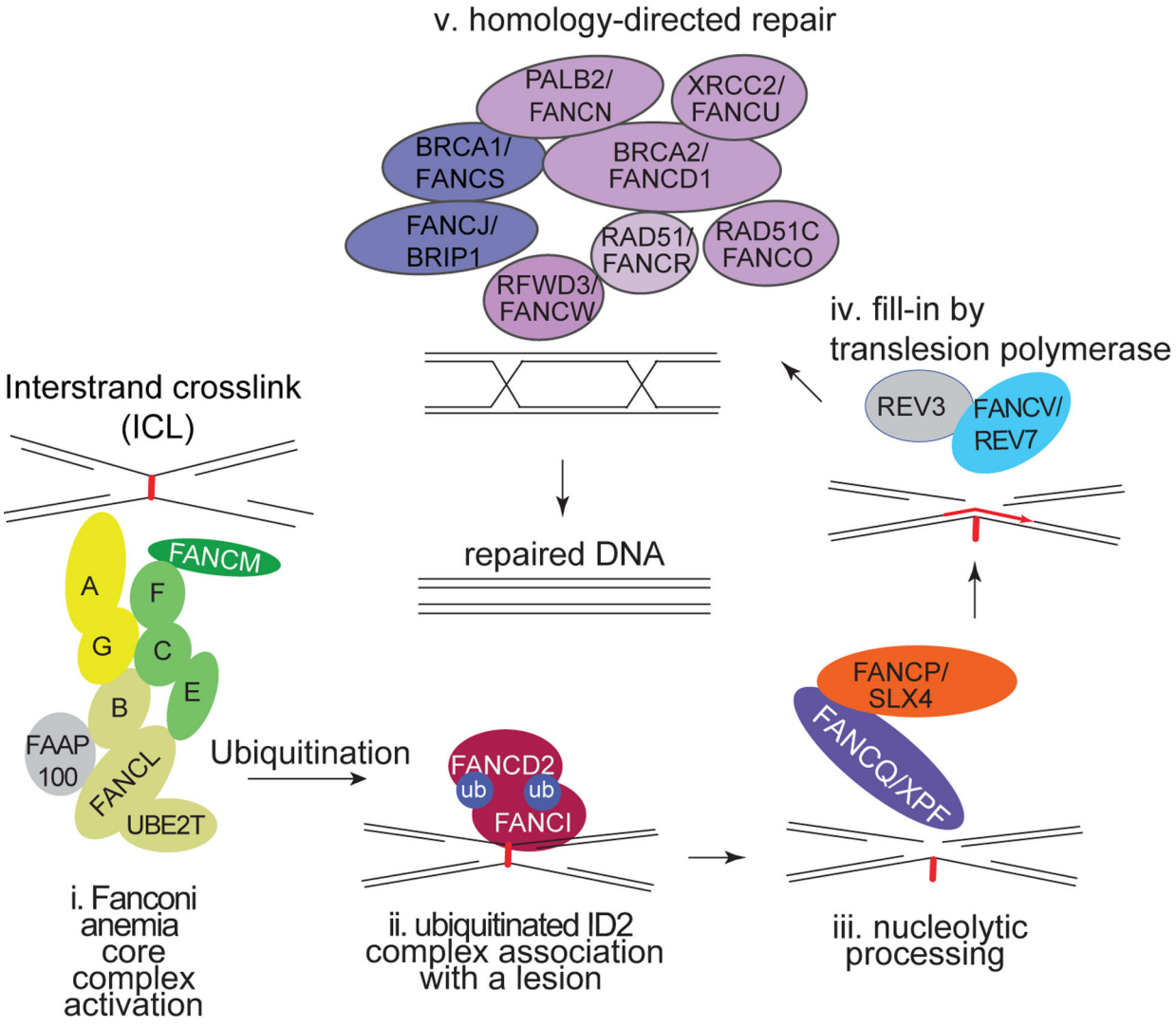


**Figure 1. Repair of DNA interstrand crosslinks.**

A series of steps, allows removal of the crosslink beginning with its recognition by the core complex (i) of Fanconi proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FANCM and FANCT). This in turn activates the ID2 complex (ii) that allows the structure specific nuclease FANQ (also known as XPF) bound to scaffold protein FANCP (also known as SLX4) to cut the DNA on one strand (iii). This is followed by a DNA synthesis step (iv) performed by the translesion polymerase FANCV (also known as REV7). The final step is involves homology directed repair (v) involving the homologous recombination repair proteins (FANCS/BRCA1, FANJ/BRIP1, FANCR/RAD51, FANCO/RAD51C, FANCN/PALB2, FANCD1/BRCA2, FANCU/XRCC2 and FANW/RFWD3).

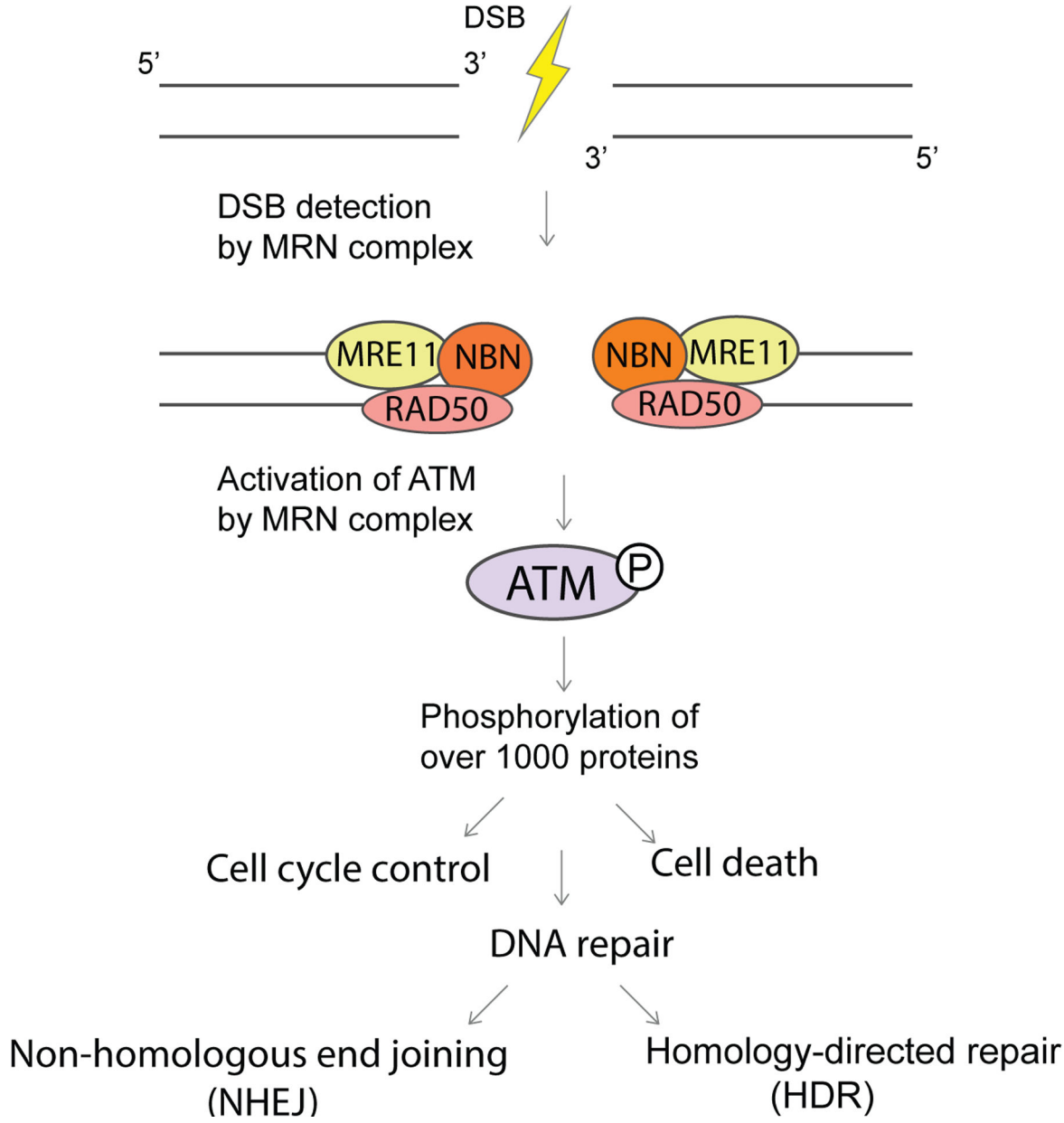


**Figure 2. DNA double strand break (DSB) repair – the role of NBN and ATM in the recognition and signalling of the breaks.**

DNA double-strand break repair. Nibrin (NBN) recognizes DNA double-strand breaks (DSBs) via its involvement in the MRN complex, which is composed of DSB repair protein MRE11, DNA repair protein RAD50 and NBN. This recognition is required to activate serine-protein kinase ATM (ATM). ATM phosphorylates many downstream proteins to regulate DNA damage response pathways that include DNA repair, which in the case of DSBs can proceed through non-homologous end-joining or homology-directed repair. Mutations in NBN are pathognomonic of Nijmegen breakage syndrome and mutations in ATM are pathognomonic of ataxia telangiectasia. ATLD, ataxia telangiectasia-like disorder; NBSLD, Nijmegen breakage syndrome-like disorder.

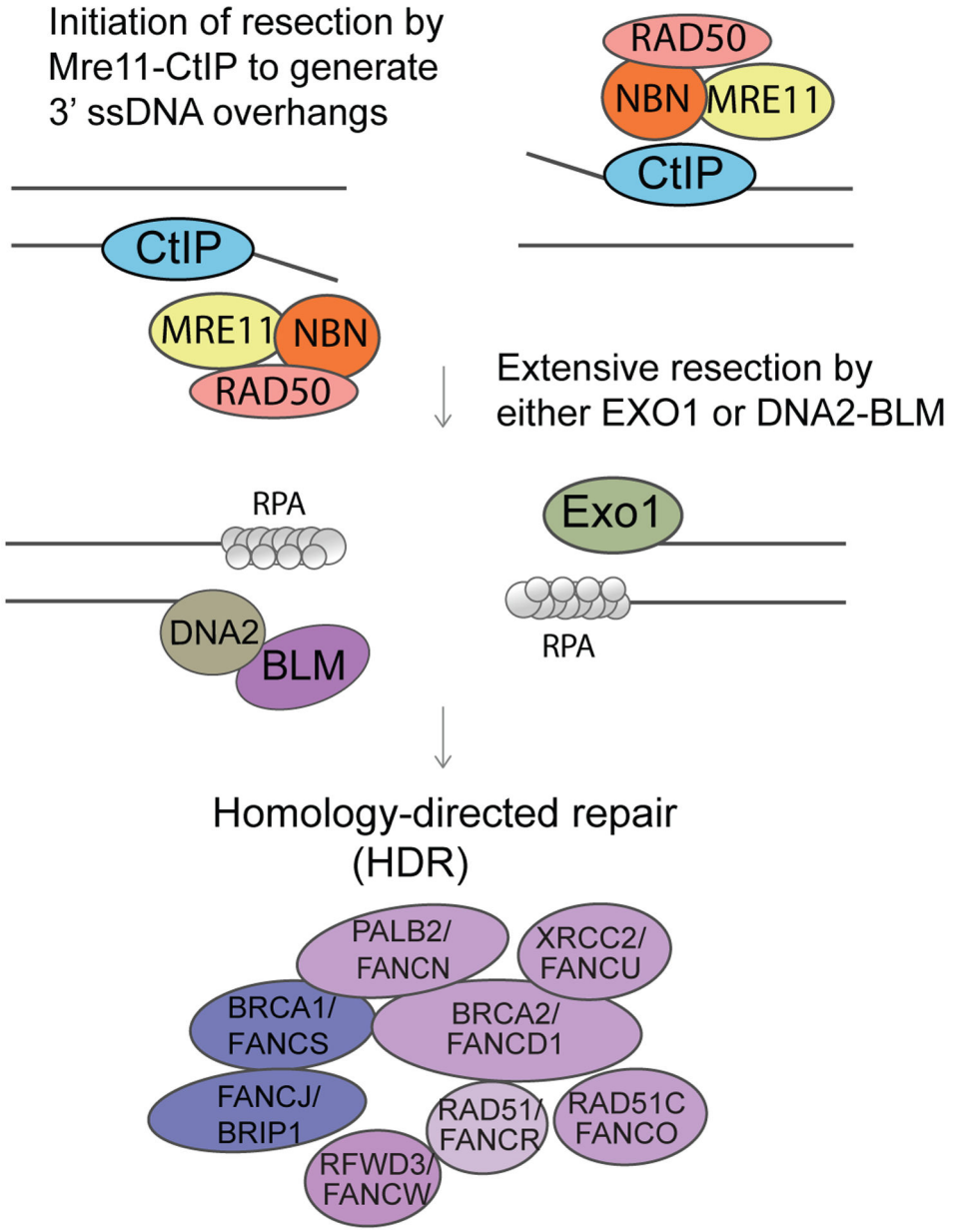


**Figure 3. DNA end resection of the 5' end.**

Undertaken by the MRN complex together with CtIP that results in RPA-3' coated ssDNA overhangs. Long-range resection is carried by the BLM/DNA2 (helicase/nuclease) complex. 53BP1 and Rif1 suppress any excessive resection. Here BLM is promoting HR. The BRCA1/FANCS, BRCA2/FANCD1, PALB2/FANCN complex allows removal of RPA and the formation of RAD51 coated ssDNA nucleofilaments that catalyse strand invasion of the unbroken homologous template. The BLM helicase can suppress HR by destabilising the RAD51 coated nucleofilaments. Recombination repair is facilitated by Rad51 and co-factors

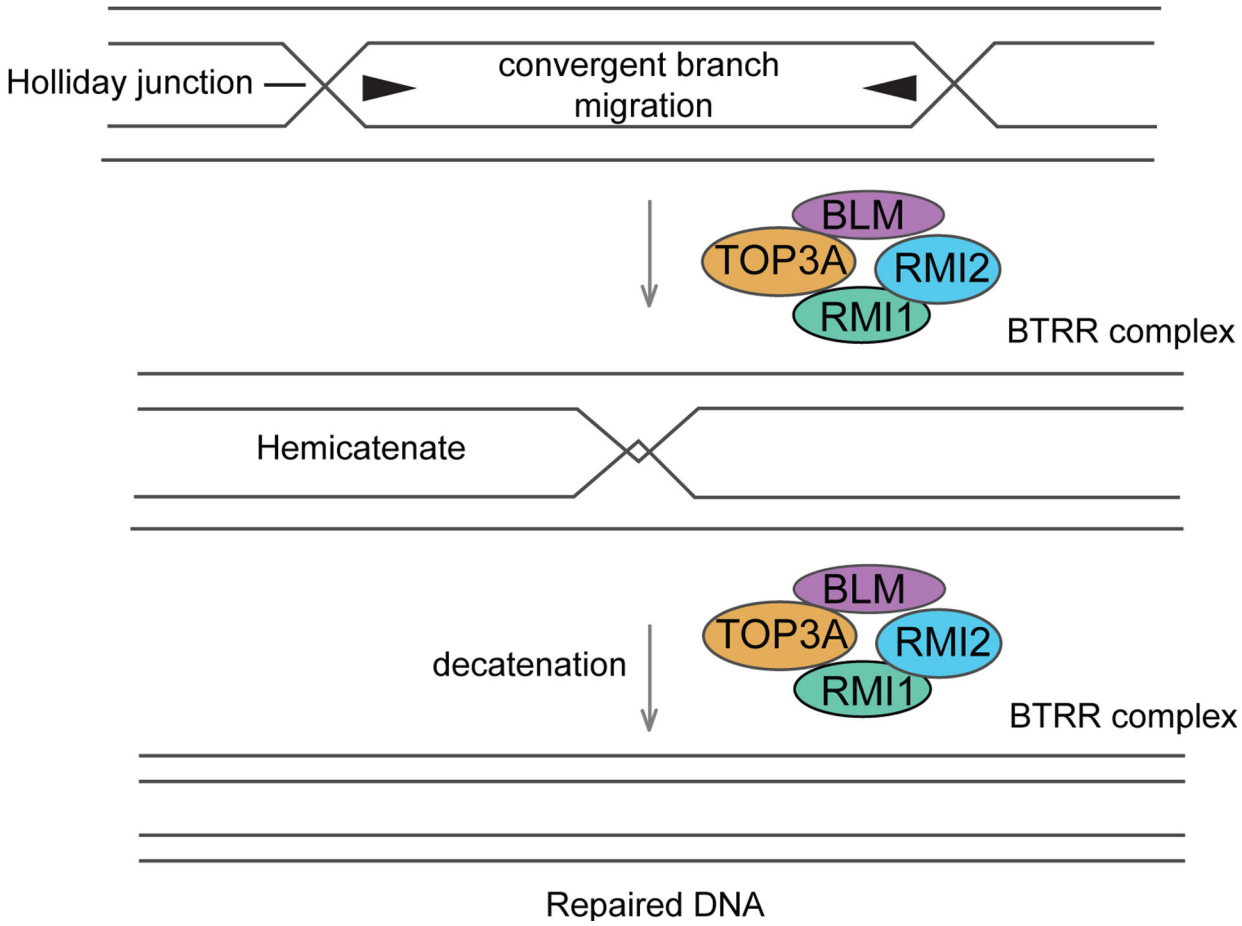


**Figure 4. Dissolution of double Holliday (dHJs) junctions.**

Mechanism of double Holliday junction (dHJ) dissolution by the combined action of the BTRR complex. BLM catalyzes convergent branch migation of the HJs to convert the dHJ into a hemicatenane, which is then decatenated by Topo IIIα.

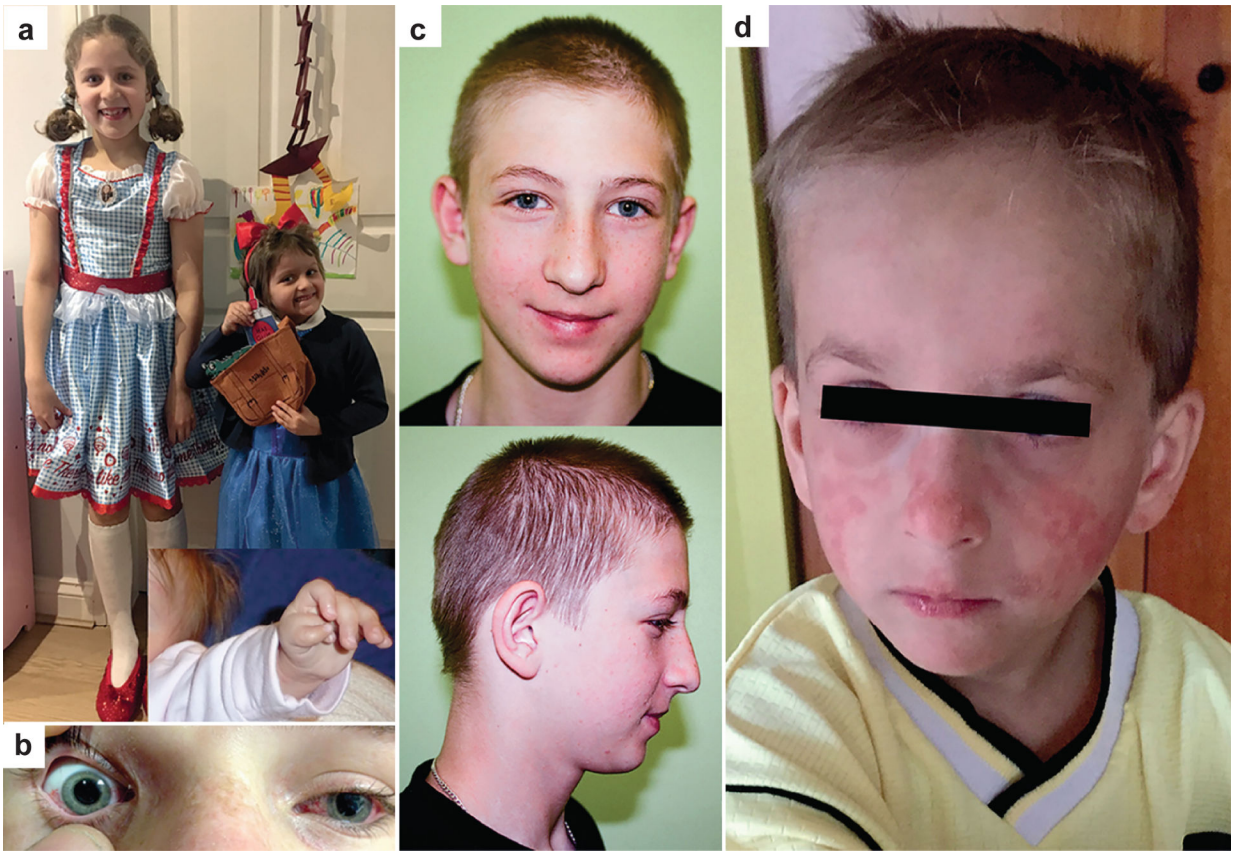


**Figure 5. Characteristic features of the chromosome instability syndromes**

Characteristic features of the chromosome instability syndromes. a. The characteristic clinical features of children with Fanconi anaemia include extreme short stature, microcephaly and mid-facial hypoplasia, as illustrated in a 5-year-old girl (right) next to her unaffected 8-year-old sister. Inset shows the duplex thumb of the affected girl before surgical correction. b. Characteristic ocular telangiectasis of the exposed, but not the unexposed, bulbar conjunctiva in ataxia telangiectasia. c. The craniofacial features of those with Nijmegen breakage syndrome include receding forehead, receding mandible and prominent mid face with long nose. d. Characteristic sun-sensitive facial erythema in a young boy with Bloom syndrome.

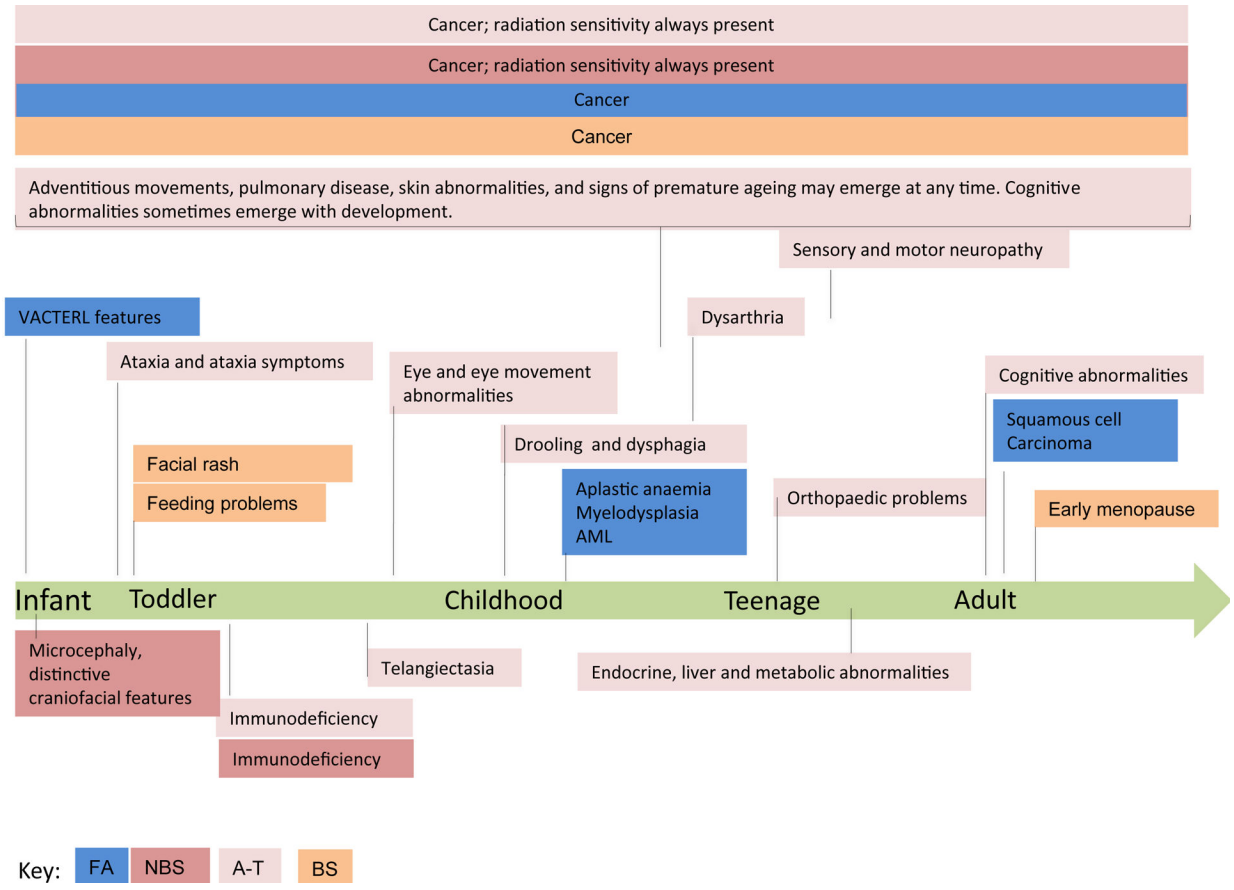


**Figure 6. The natural history of the chromosome breakage disorders.**

Each disorder has its own spectrum of age-related clinical features; in the case of most individuals with Fanconi anaemia this is focused on the consequences of bone marrow failure; in those with ataxia telangiectasia the progressive neurodegeneration and requirement for wheelchair use; in NBS the immunodeficiency and learning difficulties and in Bloom Syndrome small size and slowness with certainty about the diagnosis. All the disorders have a greatly increased likelihood of developing cancer.