Rare hereditary diseases with defects in DNA-repair

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Rare hereditary diseases with defects in DNA-repair

The human genome is constantly exposed to various sources of DNA damage. Ineffective protection from this damage leads to genetic instability which can ultimately give rise to somatic disease, causing mutations. Therefore our organism commands a number of highly conserved and effective mechanisms responsible for DNA repair. If these repair mechanisms are defective due to germline mutations in relevant genes, rare diseases with DNA repair deficiencies can arise. Today, a limited number of rare hereditary diseases characterized by genetic defects of DNA repair mechanisms is known, comprising ataxia telangiectasia, Nijmegen breakage syndrome, Werner syndrome, Bloom Syndrome, Fanconi anemia, xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy. Although heterogeneous in respect to selected symptoms, these rare disorders share many clinical features such as growth retardation, neurological disorders, premature ageing, skin alterations including abnormal pigmentation, telangiectasia, xerosis cutis, pathological wound healing as well as an increased risk of developing different types of cancer. Based on the clinical similarities of symptoms as well as the predominant diagnostic technology available, many of these rare disorders were formerly classified as genodermatoses with cancer predisposition or chromosomal breakage symptoms. These pathological conditions not only severely impair patients with these rare genetic diseases but also represent symptoms affecting large parts of the general population.

Key words: DNA-repair, premature aging, cancer, Fanconi anemia, Bloom Syndrome, Werner syndrome, ataxia telangiectasia, Nijmegen breakage syndrome, xeroderma pigmentosum, trichothiodystrophy, Cockayne syndrome

Ataxia telangiectasia *(figure 1)*

OMIM ATM: #208900

Ataxia telangiectasia (A-T) is inherited in an autosomal-recessive manner and its frequency has been estimated to be 1 per 40,000 births [1].

The first case of A-T was described in literature by Denise Louis-Bar in 1941, a case report of a 9-year-old child. In 1958 Boder and Sedgwick introduced the term ataxia telangiectasia. Sometimes A-T is also called Louis-Bar syndrome or Boder-Sedgwick syndrome.

As already indicated by the name of the disease, ataxia and telangiectasia - initially occurring in the eye, are the most apparent symptoms of A-T. Other symptoms are progressive cerebellar degeneration, immunodeficiency hypogonadism, atypical necrobiotic lesions and sensitivity to ionising radiation. The first symptoms of A-T occur in childhood, namely the development of ataxia with problems in walking and standing and most patients are bound to wheelchairs by the age of 10 years [2]. Due to a high predisposition to malignancies like leukaemia and to immunodeficiency, the average life expectancy is low [3]. Furthermore, premature aging, including an elevated incidence of diabetes mellitus and progeric hair and skin changes are symptoms of A-T [4]. Importantly, even heterozygous carriers of ATM mutations have an elevated breast cancer risk. Especially patients who smoke but also non-smokers show this elevated risk compared to non-carriers of a mutated A-T allele [5].

The causative gene is *ATM* (ataxia-telangiectasia-mutated), located on chromosome 11. The ATM-protein is a serine-threonine kinase, which plays a role in the damage induced repair of DNA, especially double strand breaks (DSB) [6], cell cycle regulation, in particular the G1 and S-phase checkpoints [7] and apoptosis [8]. Symptoms of a mouse model with ATM deficiency closely resemble the human disease, with symptoms such as increased chromosome breakage, T cell deficiencies and aspermiogenesis, further supporting that mutations in genes encoding for double strand break repair lead to the symptoms observed in human patients [9].

In the repair of DSBs, ATM is not required for about 80% of DSBs. But for the other 15-20%, ATM activity is essential for repair. DSBs that need the activity of ATM have been found to be in close proximity to

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heterochromatin-structures. ATM is needed for the phosphorylation of KAP-1 (Kruppel-associated box associated protein-1), which is a part of the heterochromatin and after phosphorylation allows access for other proteins to the site of damage [10]. Depending on the phase of the cell-cycle, ATM mediated DSB-repair either is performed by non-homologous end joining (NHEJ) in the S and G1 phases, or by homologous recombination repair (HR) in G2 phase [11]. In HR in the G2-phase, ATM is primarily needed for the phosphorylation of KAP-1 but later in HR it also activates CtIP (C-terminal binding protein interacting protein), also via phosphorylation [12]. In the G1- and S-phases, ATM is also required for KAP-1 phosphorylation. Additionally, ATM phosphorylation of KAP-1 is further enhanced by 53 BP1 activity [13].
Looking at cell-cycle and apoptosis regulation, ATM interaction partners corroborate its importance. Some of the most prominent interaction partners of ATM are, for example, p53 (protein 53), but also CHK2 (checkpoint kinase 2), BRCA1 (breast cancer 1), NBS1 (Nijmegen breakage syndrome 1), Rad17 (radiation 17) or FANCD1 (Fanconi anemia D1) as cell-cycle regulating proteins [14-17].
ATM itself can be activated by a complex of Mre11 (meiotic recombination 11), Rad 50 (radiation 50) and NBS1, the so called MRN-complex, which is also a sensor for DSBs [18, 19]. The MRN complex causes damage-induced auto-phosphorylation of ATM, which leads to dissolving of dimerized or multimerized ATM [20]. Autophosphorylation without MRN has also been observed.
Due to the large amounts of substrate and interacting proteins, which corroborate its importance, the exact regulation of ATM is still unclear. The cancer and immunodeficiency phenotype of A-T could possibly be explained by the DSB-repair deficiency and the impaired cell-cycle and apoptosis regulation.
The premature aging symptoms and the cerebellar degeneration may be due to involvement of ATM in mitochondrial function and biogenesis [21], although a primary DNA repair defect probably also plays a role in the premature aging symptoms. Another explanation for the cerebellar degeneration could be that the defective ATM protein inhibits apoptosis of damaged neural cells, which are then incorporated into the mature nervous system. Later these cells cannot tolerate the increasing damage and die [22].
Taken together, ATM is important for damage induced repair of specific DSBs, which is one reason for the elevated cancer risk and immunodeficiency in A-T patients. Additionally ATM is an important activator and regulator for many pathways, including p53-dependent apoptosis, cell cycle regulation via CHK2, BRCA1 and many others. The specific impact of ATM (respectively of ATM deficiency) on many of these protein networks is not yet clarified, but could be another reason for the cancer predisposition and could give rise to other clinical symptoms of A-T.

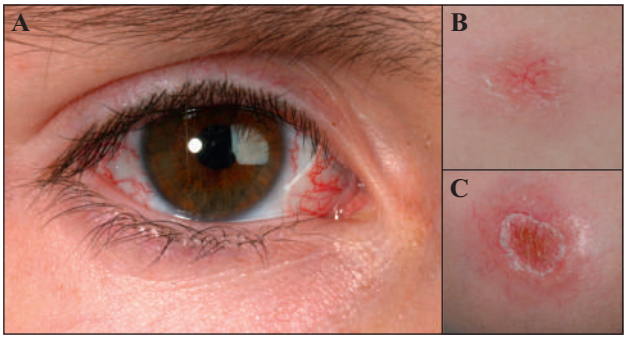

Figure 1. Clinical appearance of ataxia telangiectasia. **A)** Telangiectasia visible in the eye of a female patient with AT. **B)** Telangiectasia on the skin of the same patient. **C)** Telangiectasia accompanied with scaling of the skin.

Abbreviations:

AT	ataxia telangiectasia
ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia related
BER	base excision repair
BLAP75	BLM associated protein 75 kDa
BS	Bloom syndrome
BRCA1	breast cancer 1
CAF1	chromatin accessibility factor 1
CHK2	checkpoint kinase 2
CS	Cockayne syndrome
CtIP	C-terminal binding protein interacting protein
CUL4a	Cullin 4A
DDB1	damage specific DNA-binding protein 1
DNA-PKcs	DNA-protein kinase-catalytic subunit
DSB	double strand breaks
FA	Fanconi anemia
γ-H2AX	phosphoryated histone 2AX
HR	homologous recombination
KAP-1	Kruppel-associated box associated protein 1
MRE11	meiotic recombination 11
mt	mitochondria
NBS	Nijmegen breakage syndrome
NBS1	Nijmegen breakage syndrome 1
NER	nucleotide excision repair
NHEJ	non homologous end joining
p53	protein 53
PARP1	Poly-ADP-ribose polymerase1
Rad50, Rad54, Rad17	radiation 17, 50, 54
RNAi	RNA interference
ROC1	Rotamase Cyp 1
SCE	sister chromatid exchange
ssDNA	single stranded DNA
TCR	transcription-coupled repair
Top3α	topoisomerase IIIα
TRF2	TATA box binding protein-related factor 2
TTD	Trichothiodystrophy
UBD	ubiquitin-binding domain
WS	Werner syndrome
WRN	Werner helicase
XP	Xeroderma pigmentosum

Nijmegen breakage syndrome

OMIM NBS1: #251260

The Nijmegen breakage syndrome (NBS) was named after the Dutch city Nijmegen, where it was first described as

an independent syndrome in 1981 by Weemaes *et al*., and it was first thought to be a subform of A-T. The estimated prevalence of the autosomal recessive NBS in Germany is 1 per 3 million people [23]. Patients with NBS display typical facial features, such as a birdlike face with a receding forehead and a prominent midface, with a long nose and philtrum and a receding mandible. In the first months of life, NBS patients show a remarkedly severe and progressive microcephaly. Other symptoms are growth retardation, mild mental retardation, sun sensitivity, café-au-lait spots, clino- and syndactyly and immunodeficiency [24, 25]. NBS patients also display an elevated cancer risk, especially for lymphomas, which mostly are non-Hodgkin's lymphomas [26]. Heterozygous carriers of NBS1 mutations also have an elevated risk of developing malignant tumors such as leukemias, lymphomas, breast- and colorectal cancers [27]. NBS is caused by biallelic mutations in the *NBS1* gene on chromosome 8. Cells from NBS-patients display chromosomal instability and sensitivity to agents causing DSBs [25, 28, 29].

As already mentioned, NBS1 is part of the MRN-complex, which is an activator of the ATM-protein and also recruits ATM to sites of DNA-DSB-damage [19]. This connection of NBS1 to repair of DSBs, cell-cycle regulation and apoptosis regulation explains the clinical similarity between A-T and NBS.

The microcephaly occurring in NBS is different from the neurodegenerative phenotype of A-T. Due to the repair defect, the affected neural cells undergo apoptosis in an ATM-dependent manner. Thus, the number of brain cells is decreased, which may account for the microcephaly phenotype in NBS [22].

Taken together, NBS1 plays an important role as the DNA-DSB sensor and activator of ATM. Many of the symptoms of NBS, such as an elevated cancer risk or immunodeficiency, are shared with A-T and also have the same origin, as NBS1 and ATM are direct interaction partners. Differences from A-T may come from the functional ATM-protein, which does not always need the activation of NBS1, thus leaving some pathways unaffected, while others only associated to NBS1 may be disturbed.

Xeroderma pigmentosum *(figure 2)*

OMIM XPA: #278700 // OMIM XPB: #610651// OMIM XPC: #278720 // OMIM XPD: #278730 // OMIM XPE: #278740 // OMIM XPF: #278760 // OMIM XPG: #278780 // OMIM XPV: #278750

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease with a prevalence of $1{:}10^6$ in Europe [30]. It was first described in 1874 by Hebra and Kaposi, who in 1882 first used the rather descriptive term of xeroderma pigmentosum. Characteristic symptoms of XP-patients are xerosis and poikiloderma of the skin. Freckling of sun-exposed areas of the skin in children less than 2 years of age is unusual in healthy children and is indicated as a diagnostic marker for XP. With continued sun exposure the skin of XP-patients develops the typical appearance of poikiloderma, hypo- and hyperpigmentation, atrophy and telangiectasia

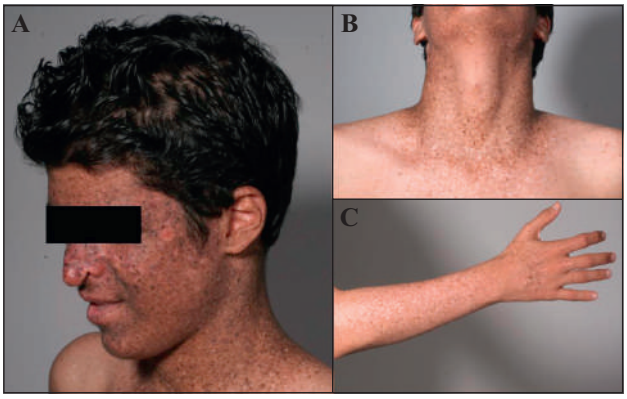

Figure 2. Clinical appearance of Xeroderma pigmentosum.
Patient with XP exhibits sharp contrast between sun-exposed and non sun-exposed areas of the skin. Sun exposed areas show telangiectasia and poikiloderma with hypo- and hyperpigmentation in contrast to sun protected shoulders. Additionally, skin shows an overall dry appearance giving the disease its name. **A)** Side view of a male patient with XP. Scars are due to tumor excisions of two squamous cell carcinomas. **B)** Chin and neck of the same patient. **C)** Right forearm of the same patient.

[31, 32]. Approximately half of the patients experience severe acute sunburn reactions after short sun exposure. The remaining XP patients do not show this sun sensitivity and develop the above described freckled phenotype after sun exposure.

Up to one third of patients show progressive neurological degeneration. First signs of neurological involvement are often the absence of deep tendon reflexes and high frequency sensorineural hearing loss. The progression of the neurological degeneration is variable. Patients may loose their coordination, their ability to walk and show intellectual deterioration, difficulties with swallowing, moreover patients may develop quadraparesis [31, 33-35].

Newer data indicate that XP is characterized by a 10,000-fold increase in non-melanoma skin cancer risk (squamous cell carcinomas and basal cell carcinomas) and a 2,000-fold increased risk of melanoma. The median age of onset of skin cancer is less than 10 years in XP-patients. The frequency of internal cancers, including tumors of the central nervous system, is also increased [36].

With regards to protection from development of skin symptoms the most important point is to protect patients from any type of exposure to natural or artificial sources of ultraviolet (UV) radiation. This is carried out by protecting the skin by long-sleeved clothing, wide brimmed hats and gloves. Patients should also apply topical sunscreen lotions with the highest protection levels in the UV-B (280-320 nm) but also in the UV-A range (>320 nm). Furthermore, protective screens should be applied to all windows at home, at work or on the cars in order to shield from any type of UV-exposure. There are two different xenogenic repair enzymes, T4 endonuclease V and photolyase. As both enzymes are now commercially available, in lotions only for T4 endonuclease V, a protective effect from the development of non-melanoma skin cancer and its precursors has been reported [37, 38].

There are eight genes, which, if defective, can cause XP. The products of these genes are referred to as XPA to XPG, or

the XP-variant XPV (also known as polymerase η (Pol η)) and in case of defects, determine the complementation group of the patients [39, 40]. Clinical symptoms can vary between complementation groups and also within a single complementation group. There are no studies available that clearly allocate specific symptoms to each known XP complementation group. Ueda *et al* recently found that the second mutations in compound heterozygous patients also influence the phenotype, thus giving a first hint as to how variations of phenotypes can be explained in patients with identical mutations in the *XPD* gene [41]. Overall complementation groups XP-A, XP-C and XP-D show generally more severe skin phenotypes than XP-E, XP-F or XP-G but more studies are necessary to substantiate this clinical observation [35, 42].

With the exception of Pol η, the XP-proteins are involved in nucleotide excision repair (NER) [43]. NER is a repair-pathway which mainly removes bulky, helix distorting DNA damage, such as cyclobutane pyrimidine dimers (CPD) and 6-4 photoproducts, which are predominantly induced by ultraviolet radiation. In addition to these lesions, DNA damage induced by cisplatin and reactive oxygen species can be removed by NER.

NER can be divided into two sub-pathways, global genome repair (GGR) and transcription coupled repair (TCR). GGR is able to repair damage in every part of the nuclear genome. In this sub-pathway a complex including XPE (DDB2) recognizes the damage and recruits an XPC-containing complex to the damaged site. In TCR the RNA-polymerase II gets stalled by damaged DNA and then strengthens its interaction with CSB. This leads to the recruitment of XAB2 and a complex containing the CSA-protein to the damaged site. After damage recognition, the further steps of GGR and TCR employ the same protein-complex consisting of XPA, and RPA binds to the damaged region and recruits XPB and XPD as parts of the transcription factor IIH (TFIIH) complex. XPB and XPD helicases then can open the DNA-strand, which then enables the XPF-ERCC1 and the XPG endonucleases to excise the damaged strand. Afterwards the gap can be filled by DNA-polymerases [31].

Another role for many NER-proteins was found in transcription. The proteins XPB and XPD play a role in transcription as they are part of TFIIH, which is important for the initiation of transcription and transition from initiation to elongation [44].

Furthermore, the proteins XPA, -B, -C, -D, XPF-ERCC1, XPG as well as CSB are sequentially recruited to promoter sites of active genes in unstressed cells. Le May and Mota-Fernandes *et al*. were able to demonstrate that these proteins, except for CSB, are needed for chromatin-remodelling, which is needed for proper RNA-synthesis. CSB-deficient cells showed no impairment of recruitment of the proteins to promoter-sites and no defects in RNA-synthesis [45].

Interestingly, patients with defects in XPV/Pol η have intact repair of UV-induced or oxidative DNA-damage but they are defective in translesion synthesis. In healthy individuals, pol η is able to carry out translesion synthesis during DNA replication [46], which means that, during the polymerisation process, this polymerase is able to read through damaged template DNA with lesions coming from internal or external sources of damage. In the case of defective XPV, replication of DNA with e.g. UV-induced lesions is disturbed and other polymerases with a higher rate of mistakes are thought to take up this task [47], thus resulting in a mutator phenotype that generates skin symptoms similar to NER-defective XP cells.

There are numerous well characterised mouse models covering the phenotypes of different XP complementation groups, Cockayne syndrome and trichothiodystrophy. Additionally, animals carrying more than one mutation of the known NER genes are also available. All these animals provide excellent models for investigating the different clinical phenotypes observed in the three different NER deficient disorders [48, 49]. Taken together, the XP proteins, except for XPV, play an important role in the repair of oxidative and UV-induced DNA damage. XPV is needed for proper translesion synthesis during recombination and so all eight XP-proteins are needed to prevent DNA mutations.

Most of the XP-proteins (exceptions are XPV and XPE) are also involved in transcription as chromatin remodelling factors and in the cases of XPB and XPD, also in basal transcription.

Except for photosensitivity, which may originate from the repair defect, it is still not clear which of those functions are the reason for the elevated cancer risk and which account for neurodegeneration or the other XP features.

We believe that the elevated cancer risk may be due to the NER failure, while other symptoms could stem from transcriptional defects due to impaired TFIIH and due to the recently found chromatin remodelling activity.

Trichothiodystrophy

OMIM Trichothiodystrophy (photosensitive): #601675. // OMIM Trichothiodystrophy (not photosensitive): #234050

Trichothiodystrophy (TTD) is an autosomal recessive disease with a prevalence of about one per million births in Europe for the photosensitive variant of TTD [30]. It was first described by Tay in 1971. Later, in 1976 acronyms were introduced where BIDS stands for Brittle hair, Intellectual impairment, Decreased fertility and Short stature. Over time this term was expanded to PIBIDS by Photosensitivity and Ichthyosis. Due to the large clinical heterogeneity, and since most of the causative mutations have been identified, this terminology is no longer widely used. The same is true for the term Tay syndrome, which describes a severe subtype of TTD [50, 51]. Onset of the disease may be observed directly after birth, where babies can have a collodion membrane, or in early childhood [52].

The clinical hallmarks of TTD are the characteristic sulphur-deficient brittle hair and nails. Marked photosensitivity, ichthyosis, neurological and skeletal degeneration as well as growth and mental retardation are also possible symptoms. The clinical features of TTD show great variation in form, expression and severity.

In TTD there are three complementation groups. Mutations in the *XPD*, *XPB* and the *TTDA*-genes can give rise to TTD. In most TTD-patients the *XPD* gene is mutated and the location of the mutation defines the phenotypical outcome [31]. The TTDA gene is the smallest member of the TFIIH complex and is needed for the stability of the TFIIH complex [51, 53].

In some cases TTD occurs without photosensitivity. In these patients with TTD but without photosensitivity, a mutation of the *TTDN1* gene has been observed as cause of TTD symptoms. The TTDN1 protein as substrate of Cdk1 and its interaction with Plk1 point to a role in the maintenance of mitosis and cell-cycle integrity [54], but it is unclear whether defects in this function of TTDN1 can account for TTD. The genetic relevance of TTDN1 mutations is not yet clarified.

The proteins, which when defective cause photosensitive TTD, are part of the transcription-factor TFIIH (transcription-factor IIH), which is important for basal transcription but also plays a role in the nucleotide excision repair (NER) [55]. Although the mutations leading to TTD in part occur in the same genes mutated in XP, patients with TTD show no elevated cancer risk.

A number of authors have proposed that mutations affecting the NER lead to XP and mutations affecting basal transcription lead to TTD [56-58]. Other explanations for this clinical difference range from altered temperature-sensitivity in transcription [59] to differential repair of CPDs and 6-4PP [60, 61]. In 2008, Boyle *et al.* discovered that there is a difference in the localization and recruitment of the NER proteins, affected by different mutations. In XP- (XPD), TTD- (XPB, XPD and TTDA) and WT- (wild type) cells, XPC was rapidly found at the damaged site. The recruitment of further NER proteins was delayed in XP and in the TTD-cells. In XP cells, the NER proteins were recruited and assembled at the damaged site, but due to the mutation in one of the proteins, the complex persisted in the DNA. This persistence was still observed 24h post irradiation, which was the origin of the damage [62]. Similarly, in XPB-cells, persistence of NER-proteins could also be observed 24h after irradiation at the damaged site [63]. The TTD cells, additional to the delayed recruitment, showed only little recruitment of NER proteins, maybe due to an unstable TFIIH complex. The damage was still not repaired 24h post irradiation and no NER proteins were detectable at that time point [62]. It was therefore concluded that mutations in the *XPB*, *XPD* and *TTDA* genes, which cause the TTD phenotype, are associated with failure of TFIIH and lead to defects in TFIIH-associated basal transcription and nucleotide excision repair. To summarize, the TTD-proteins belong to the TFIIH complex and are important factors of NER and basal transcription. Presumably the defects in this form of TTD, except for the photosensitivity, are mainly connected to the basal transcription deficiency. The photosensitivity may stem from the NER-defect and therefore does not occur in patients with mutations in *TTDN1*.

TTDN1 is connected to Cdk1 and Plk1 and thus to maintenance of mitosis and cell-cycle integrity. However it is still unclear how TTDN1 defects lead to the TTD-phenotype and how the different types of TTD are related.

Cockayne syndrome

OMIM CSA: #216400 // OMIM CSB: #133540

Cockayne syndrome (CS) is inherited in an autosomal recessive way. This rare disease occurs in 1/250,000 births [30]. Onset of CS ranges from birth up to the age of two years. It was first described in 1933 by Edward Cockayne, a London physician.

The symptoms of CS comprise mental and developmental retardation as well as photosensitivity. Other signs are progressive sensorineural hearing loss, short stature, a typical bird-like face, progeria (cataracts and graying), deep-set eyes, loss of subcutaneous fat, microcephaly and progressive neurological degeneration. Patients display signs of premature ageing and progressive neurodegeneration with demyelination of the brain stem and cerebellum [34].

CS can be caused by defects in the *CSA* or *CSB* genes, but also mutations in *XPB*, *XPD* or *XPG* alone can be found, causing a combination of CS and a CS-XP-complex phenotype. The CSA and CSB proteins play a role in a subpathway of the NER, the transcription-coupled repair (TCR), where CSB plays a role in damage recognition, after RNA-polymerase II has been stalled by helix-distorting DNA-damage and further recruitment of proteins. CSA belongs to a complex including ROC1 (Rotamase Cyp 1), CUL4a (Cullin 4A) and DDB1 (damage specific DNA-binding protein 1). This complex has an ubiquitin-ligase activity. The ubiquitination is needed for further course of TCR. A recently discovered ubiquitin-binding domain (UBD) at the CSB-protein points to a connection also between the ubiquitination, CSB and the further progression of TCR. Furthermore the UBD has been shown to be important for incision or excision of the damage-site, which does not occur in cells where the CSB-protein lacks this UBD [64].

Although some proteins causing XP are also engaged in the TCR-pathway, CS patients do not show the elevated cancer-risk which comes along with XP. The engagement of CSA and CSB in TCR is sufficient to explain some (sun sensitivity or sensorineural hearing loss) but not all the symptoms of CS. Short stature, cataracts, brain calcification, neurodegeneration and premature aging are symptoms which are often found in mitochondriopathies and they may point to an additional role for mitochondria in CS. Recently it was shown that CSA and CSB translocate to the mitochondria after oxidative damage. It was also demonstrated that CS-proteins are present in a complex with the mitochondrial version of proteins belonging to the base excision repair pathway (BER) [65]. Furthermore, the CSB-protein has been found to interact with APE 1 (apurinic/apyrimidinyc site endonuclease 1) and hOGG1 (human 8-oxoguanine DNA glycosylase), both proteins belonging to the BER [66, 67].

Taken together, the CS-proteins are involved in signalling of the TCR-part of NER, which is the reason for the photosensitive phenotype of CS. Furthermore, they localize to mitochondria after oxidative stress, where they further interact with mitochondrial proteins to protect the cell from oxidative stress-induced damage. In case of defect, this may contribute to the prematurely aged and mitochondriopathy-like phenotype in CS.

Werner syndrome

OMIM WRN: #277700

Werner syndrome (WS) is inherited in an autosomal recessive manner and can be found in 1 in a million individuals.

This syndrome was first described by Otto Werner in 1904. Patients with WS suffer from the premature development of aging symptoms. Children are born normal and develop aging symptoms after puberty. Characteristic symptoms of WS are ulceration of the skin, scleroderma-like, atrophic skin, loss of subcutaneous fat tissue, premature graying and loss of hair, osteoporosis, cataracts, diabetes, atherosclerosis and elevated cancer risk. [68-70]. The cancer forms mainly occurring in WS are sarcomas, carcinomas and haematological malignancies.

WS is typically caused by mutations in the *WRN* gene on chromosome 8, although a few rare patients with Werner-like symptoms have been reported who have a mutation of the lamin A/C gene [71, 72], also implicated in the very early onset form of progeria called Hutchinson Guilford progeria [73]. The *WRN* mutations leading to a truncation, a destabilization or a complete loss of the WRN protein are often found in two important functional regions of the WRN gene. Firstly, this is a region encoding a 3'→5' exonuclease and secondly a region including an ATPase-helicase. However, other types and locations of mutations have also been described [74].

The WRN helicase also belongs to the group of RecQ helicases and plays multiple roles in maintaining genome stability. It is able to unwind forked and bubble structures of DNA.

WRN has been found to play a role in HR repair, as it is able to bind to replication forks and Holliday junctions [75]. It also plays a role in NHEJ, which is needed for the repair of double strand breaks (DSB) [76]. WRN is the only RecQ helicase with 3'→5' exonuclease activity. This exonuclease activity of WRN is rather weak but can be stimulated by the Ku-protein complex, which belongs to the NHEJ pathway. Then WRN is able to digest bubbles, stem loops, and three-way and four-way junctions (Holliday junctions) [77]. In this context, interaction of WRN with the DNA-PK (DNA-protein kinase) subunits Ku 70 and Ku 80 [78] also points to a role in telomere maintenance, which was recently confirmed in a study by Rika Kusumoto-Matsuo *et al,* who showed that the cooperation of WRN and DNA-PKcs (DNA-protein kinase-catalytic subunit) is important for maintenance of the telomeric D-loop [79]. Additionally, the interaction of WRN with proteins belonging to the base-excision-repair (BER) pathway has been observed. WRN has been found to interact with PARP1 (Poly-ADP-ribose polymerase 1) and polymerase β (Pol β). The exonuclease activity of WRN can then act in conjunction with Pol β, which has no intrinsic 3'-5' proofreading activity. These protein complexes are able to process DNA containing 3' mispairs, to prepare for further synthesis and ligation via BER. [80].

It is unclear if the WRN protein is a true tumorsupressor-gene. In some tumors, such as colon carcinomas, WRN was found to be downregulated by epigenetic methylation [81], while it was upregulated in other types of cancer [82], corresponding to patients with functional WRN. Furthermore, WS cells show an accumulation of replicative senescence, which is probably due to their premature exit from the cell cycle [83].

Maintenance of telomere length might be dependent on WRN, as it may be able to make telomeres accessible for replication or repair by resolution of their DNA-structures [84]. Another hint for WRN influence on telomere maintenance is its interaction with the telomere capping protein TRF2 (TATA box binding protein-related factor 2), which, together with WRN, is needed for regulation of telomere maintenance and homology-dependent recombination repair [85].

Taken together, defects in WRN lead to errors in DSB-repair and telomere maintenance. The disturbance of telomere maintenance could possibly lead to senescence and to the senescence-induced tissue dysfunction which can be found in WS cells and may be the reason for the aging phenotype in WS patients. The elevated cancer risk in WS patients may be due to a high mutational load induced by dysfunctional DSB-repair.

Bloom syndrome

OMIM BLM: #210900

Bloom syndrome (BS) is an autosomal-recessive inherited disease. The prevalence is extremely rare with only about 220 cases - mostly of Ashkenanzi-Jewish origin - confirmed worldwide since 1975 [86]. It was discovered and described by the dermatologist David Bloom in 1954.

The main symptoms of BS are photosensitivity of the skin, café-au-lait macules, short stature, narrow face, male infertility, a high and pitched voice, hypogonadism, immundeficiencies, chronic lung problems, learning disabilities and a cancer predisposition, especially for non-Hodgkin's lymphoma, leukemia, and skin tumors [87]. The mean age of cancer diagnosis is about 24 years.

Patients with BS carry mutations in the BLM-gene and mice with *Blm*-deficiency are prone to haematological malignancies upon irradiation, thus mimicking the human disease [88]. The tumor-supressor gene BLM belongs to the group of RecQ helicases and contains a conserved 3'-5' helicase domain. RecQ helicases are involved in translesion synthesis and removal of mutations during DNA replication, and therefore contribute to genome maintenance. The 3'-5' helicase domain of the BLM-helicase is able to unwind 3' tailed duplexes, bubble structures, fork duplexes, G-quadruplex structures, DNA-displacement loops (D-loop) and four-way-junctions. Furthermore, BLM contains a nuclear localisation signal domain and an annealing function, which is inhibited in the presence of ATP [77].

BLM seems to have multiple roles in damage recognition. It interacts with the MRE11-Rad50 (radiation 50)-NBS1-complex, and is phosphorylated by ATM and ATR (ataxia telangiectasia related) post damage. These proteins are known to belong to the repair of DSBs. Further details pointing to a role of BLM in damage recognition are the induction of BLM after γ-irradiation, delayed assembly of NBS1 and BRCA1 (breast cancer1) repair complexes at stalled replication forks, and BLM co-localisation with ATM and γ-H2AX (phosphorylated histone 2AX) at laser induced DSBs within 10 seconds [89]. BLM is also found to play a role in resolution of DNA intermediates arising at homologous recombination (HR) where it interacts with Rad51 (radiation 51).

In HR, BLM plays a double role, depending on the phase of HR. In early HR phases, BLM acts as disruptor of the connection between Rad51 and ssDNA and thus disrupts the beginning of HR [90]. In later phases BLM has been shown to be able to unwind D-loops [91, 92], to catalyze

regression of model-replication forks [93], to recognize Holliday junctions and promote their branch migration [94], as well as to resolve double Holliday junctions [95] by forming a complex with Top3α (topoisomerase IIIα) and BLAP75 (BLM associated Protein 75 kDa) [96, 97].
Cells with defective BLM show a high frequency of reciprocal sister chromatid exchanges (SCE) and exchanges between homologous chromosomes [87]. Furthermore, BLM may have an effect on chromatin-remodelling via its effect on CAF1 (chromatin accessibility factor 1) [98] and via the stimulation of Rad 54s (radiation 54) chromatin remodelling activity [99].
In summary, BLM plays an important role in homologous recombination as it can stop the prosecution of recombination after damage, but can also resolve structures that would disturb normal recombination. Thus, defective BLM disturbs many processes concerning chromosome integrity and cell division. Furthermore, it plays a role in chromatin remodelling which is needed for proper transcription. Impairment of BLM has a strong impact on cell integrity as recombination in the event of damage is no longer suppressed efficiently, this being a reason for the high number of SCE and exchanges between homologous chromosomes, leading to the cancer predisposition, photosensitivity and immunodeficiency of patients. The further symptoms of BS may be due to disturbance of other pathways somehow interacting with BLM.

Fanconi anemia *(figure 3)*

OMIM FANC-A: #227650 // OMIM FANC-B: #300514 // OMIM FANC-C: #227645 // OMIM FANC-D1: #605724 // OMIM FANC-D2: #227646 // OMIM FANC-E: #600901 // OMIM FANC-F: #603467 // OMIM FANC-G: #614082 // OMIM FANC-I: #609053 // OMIM FANC-J: #609054 // OMIM FANC-L: #614083 // OMIM FANC-M: #614087 // OMIM FANC-N: #610832

Fanconi anemia (FA) is an X-linked or autosomal recessive inherited disease with an incidence ranging from 4 to 7 patients per one million births [100]. FA was first described in 1972 by the Swiss paediatrician, Guido Fanconi, in a case report of 3 brothers.

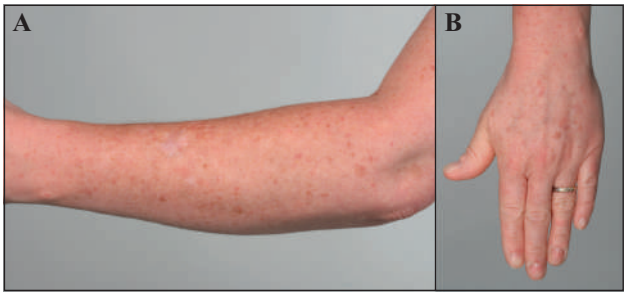

Figure 3. Clinical appearance of Fanconi anemia with poikilodermatic skin showing hypo- and hyperpigmentation of a female patient.
A) Left forearm. **B)** Left hand.

The onset of this disease is in the first decade of childhood with infantile aplastic anemia as the first symptom. In the subsequent course of the disease, patients develop tumors such as lymphomas, esophageal carcinomas, squamous cell carcinomas of the head and neck, liver and brain tumors and acute myelogenous leukaemia [101]. The skin shows a poikilodermatic appearance with hypo and hyperpigmentation and telangiectasia. Further symptoms of FA are bone marrow failure and myelodysplasia.
Mutations in several genes can give rise to FA. The patients are classified in so called complementation groups, depending on which gene is mutated. Together, FA-proteins form a DNA-damage activated signalling pathway, the so called FA-pathway. Eight of the FA-proteins (FANC-A, B, C, E, F, G, L, and M) form a core complex which shows an E3-ubiquitinase activity. This complex is able to mono-ubiquitinate the FANC-I-FANC-D2 (I-D) protein complex. I-D is then able to co-localize with FANC-D1, FANC-N and FANC-J at foci of DNA-damage [102-104]. Cells with defects in one of the FANC-proteins show accelerated telomere shortening due to increased breaking and are hypersensitive to cisplatin, a substance causing DNA interstrand crosslinks [105].
Recently, the FA-pathway has been shown to promote replication-dependent DNA interstrand crosslink repair. Especially, the incision near the interstrand crosslink and the translesion synthesis are severely inhibited in the absence of the (ubiquitinated) I-D complex [106]. The defects in DNA-repair provide a rationale to explain the elevated cancer risk of FA-patients. But they are not sufficient to explain the blood or bone-marrow defects. The exact way these defects arise is not completely understood. The use of RNAi (RNA interference) of FANC-A and FANC-D2 in human embryonic stem cells showed a reduction in hematopoietic progenitor cells, which could be rescued by the addition of the corresponding proteins [107]. Single knockout of the murine FANC-homologs did not display the blood or bone-marrow-based symptoms. A double-knockout-mouse lacking FANC-C and FANC-G did show those symptoms and indicated the role of FANC-C and FANC-G in normal hematopoiesis. [108]. This indicates that FANC-proteins possibly play an early role in the embryonic formation of a hematopoietic system, thus explaining the blood and bone marrow symptoms.
Taken together, FA-pathway proteins play a role in DNA-repair as they localize to DNA-damage foci, are involved in interstrand crosslink repair and telomere maintenance. Furthermore it appears that FANC-C and -G are involved in pathways of leukaemia associated processes.

Repair pathways and cross-reactions *(figure 4)*

All the above described diseases have defects in molecular pathways, which are involved in the repair of DNA-damage or protection from DNA-damage in sensitive processes. ATM, NBS1, BLM and WRN play a role in the repair of DSBs; BLM and WRN are also needed for proper homologous recombination; the FANC-proteins are important for the repair of interstrand-crosslinks; the CS-proteins are associated with the NER and mitochondrial and nuclear

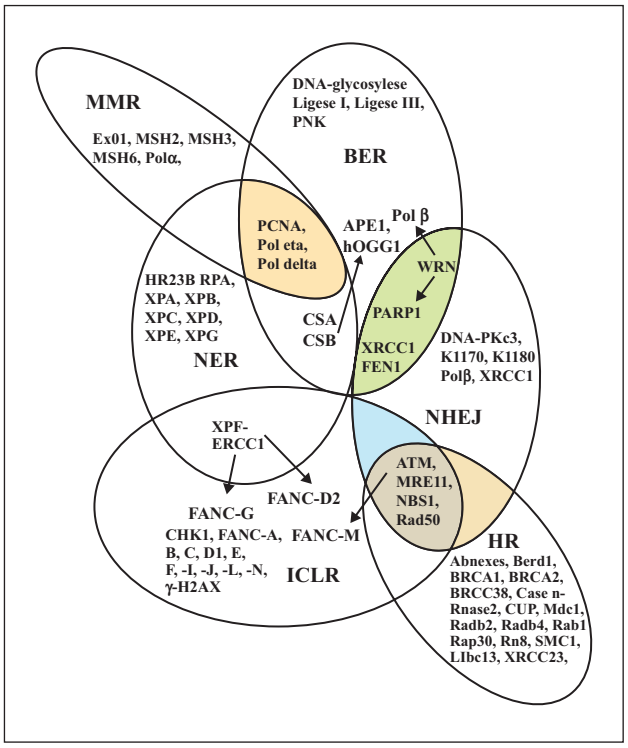

Figure 4. Proteins involved in the different repair pathways. Arrows denote interactions of proteins across different repair pathways.

BER; the XP-proteins only with NER, but they also have other tasks in transcription.

All of these rare diseases display either symptoms of premature aging and/or an elevated cancer risk. All these diseases and symptoms arise from defects in these repair proteins. The differences partly arise from different repair pathways, but also can stem from the additional tasks of the appropriate proteins. Some of these tasks also were displayed in the previous sections, here we want to introduce some others and also show cross-talk between the particular pathways.

Some of the proteins, namely the CS-proteins, the FA-proteins, A-T and WRN have been shown to be connected to the mitochondria (mt) or mitochondrial function. In A-T deficient cells, evidence has been found for intrinsic mitochondrial dysfunctions as membrane potential, respiratory activity, number of mitochondria, expression of mitochondria-targeted proteins and structural organisation of mitochondria were altered compared to WT-cells [109]. Additionally, mitochondrial biogenesis was shown to be an ATM-dependent and an AMPK (AMP-activated protein kinase) mediated process, which is activated by ROS (reactive oxygen species) induced DNA damage [21].

Finally, fibroblasts of A-T patients showed mtDNA-depletion, dysregulation of ribonucleotide reductase, increased mt transcription factor-A (mtTFA)/mtDNA ratios, increased resistance to inhibitors of mitochondrial respiration and translation. This suggests an altered energy metabolism, increased ROS-production and altered apoptosis susceptibility [110]. FANC-G was found to interact with the mitochondrial peroxiredoxin3 (PRDX3) peroxidase in mitochondria. In FANC-A, FANC-C and FANC-G cells, PRDX3 is cleaved by a calpain-like cystein protease and thus removed from its physiological localization. In FANC-G cells mitochondrial structures are distorted, sensitivity to H_2O_2 is suppressed and they show decreased thioredoxin-dependent peroxidase activity [111].

The FANC-C protein has been shown to play an important role in response to oxidative stress as it interacts with NADPH cytochrome P450 reductase, which is associated with increased ROS production [112]. FANC-C also interacts with glutathione S-transferase, which catalyzes conjugation of reduced glutathione with substrates such as chemical carcinogens, environmental pollutants or secondary metabolites formed during oxidative stress [113].

Furthermore, all kinds of FA cells show resistance to rhodamine-1,2,3 or doxycycline treatment, as well as sensitivity towards 2-deoxy-D-glucose and iodoacetic acid (glycolysis inhibitors) [114].

Mitochondrial matrix densification following 8-MOP (methoxypsoralen) photoreaction or UVA-irradiation in an O_2 dependent manner could be observed in FA-fibroblasts, as well as changes in the transmembrane potential and cardiolipin content [115].

In CS, many of the symptoms point to mitochondrial involvement, as they are similar to phenotypes of mitochondriopathies. Further mitochondrial repair of 8-oxoguanine was found to be impaired in CSB deficient cells [116]. And finally, both the CSA and CSB proteins have been shown to translocate into the mitochondria after oxidative stress. In mt they interact with mt-SSBP1 and mt-OGG1, both repair-associated mt proteins [65].

For WRN, a link to mitochondria is considered because of findings that connect WRN deficiency to oxidative stress and there are publications pointing to an at least indirect connection of WRN and mitochondria [117]. It will be interesting to see in the future whether all of these diseases are linked by their deficiency in protection from oxidative stress.

Furthermore, there are some examples for overlapping functions of proteins, which fulfil tasks in more than one repair pathway. One example of such a crosstalk is the connection between XPF-ERCC1 and proteins of the FA pathway. FANC-G has been shown to interact with the XPF-ERCC1-endonuclease and to be involved in the ICL-incision step performed by XPF-ERCC1 [118]. Furthermore in cells lacking XPF-ERCC1, FANC-D2 is found to persist longer in a mono-ubiquitinated state, bound to chromatin, and thus the further recruitment of repair proteins is impaired [119]. So proteins of ICL repair work together with a protein complex known from NER.

Another example of connections between repair pathways is ATM. It is found interacting with several proteins of other pathways. After radiation ATM phosphorylates BLM. If this phosphorylation is impaired, the cells show increased radiation-induced aberrations but no increased sister chromatid exchanges [120]. WRN has been found to modulate ATM activity during the S-phase checkpoint in response to replication-dependent DSBs [121]. Conversely, ATM and ATR have been shown to regulate WRN in order to promote replication fork recovery after DSBs [122]. Furthermore FANC-M appeared to be controlled by the ATM/ATR-pathway in extracts of *Xenopus* eggs [123].

Taken together, an increasing number of publications indicate that practically all repair pathways may be involved in

Table 1. Characteristics of different rare diseases with defects in DNA repair

Disease	Frequency	Symptoms	Age of onset	Repair pathways affected and protein functions	Affected proteins	Other known interaction-partners
Ataxia telangiectasia	1/40000-1/100000	Ataxia, telangiectasia, progressive cerebellar degeneration, immunodeficiency, hypogonadism sensitivity to ionising radiation, predisposition to cancer	Early childhood	Repair of double strand breaks, cell-cycle regulation, apoptosis	ATM-protein	ERK1 and ERK2, CHK2, p53 NBS1, MYC, FANC-D2, RAD 17, NEMO
Nijmegen breakage syndrome		Birdlike face, severe progressive microcephaly, growth retardation, sun sensitivity, café au lait spots, clino- and syndactyly and immunodeficiency, elevated cancer risk	First months of life	Repair of double strand breaks, cell-cycle regulation	NBS1 (“nibrin”)	WRN, ATM, BRCA1, SIRT1
Xeroderma pigmentosum	1/100000	Skin photosensitivity, pigmentary lesions, elevated cancer risk for skin and internal cancers, skin telangiectasia, ocular changes and mental retardation	Variable	All XP-proteins have functions in NER and in transcription (as chromatin remodelling complex). In XPV (Pol eta) is deficient and thus cannot perform translesion synthesis	XPA-, XPB-, XPC-, XPD-, XPE-, XPF-, XPG-, XPV (= Pol-eta)-protein	FANC-G
Trichothiody-strophy	1/900000	Sulphur-deficient brittle hair and nails, neurological and skeletal degeneration, marked photosensitivity, growth and mental retardation, ichthyosis	Early childhood	Basal transcription and nucleotide excision repair (TTDN1 seems to be connected to mitosis and cell-cycle maintenance)	TTDA, XPB, XPD and TTDN1	
Cockayne syndrome	About 1/400000	Mental and developmental retardation, photosensitivity, progressive sensorineural hearing loss, short stature, a typical bird like face, deep-set eyes, loss of subcutaneous fat and, premature ageing and progressive neurodegeneration and demyelination of the brain stem and cerebellum	First years of life	Nucleotide excision repair, connected to mitochondrial base excision repair, XPB, -D and -G also play a role in transcription	CSA(=ERCC8) or CSB(=ERCC6), maybe combined with XPB, XPD, XPG	In the nucleus: Pol in the mitochondria: mt-SSB, mt-OGG1
Warner syndrome	About 1/1000000	Premature development and aging, thick torso, thin arms and legs, a bird like face, ulceration of the skin, scleroderma-like, atrophic skin, loss of subcutaneous fat tissue, premature graying and loss of hair, osteoporosis, cataracts, diabetes, atherosclerosis and elevated cancer risk	After puberty	Homologous recombination, double strand break repair, telomere maintenance	WRN-Protein	NBS1, PCNA
Bloom syndrome		Café au lait macules, short stature, narrow face, male infertility, a high, pitched voice, hypogonadism, immunodeficiencies, chronic lung problems, learning disabilities and highly elevated cancer risk	For cancers: 2-49 years	Homologous recombination	BLM-protein	RAD54, ATM, ATR, NBS1 53BP1, CHK1, CHK2
Fanconi anemia	about 1/360000	Infantile aplastic anemia, cancers	First decade of life	FA-Pathway: DNA-intercrosslink-repair and translesion synthesis	FANC-A, FANC-B, FANC-C, FANC-D1(=BRCA2), FANC-D2, FANC-E, FANC-F, FANC-G, FANC-I, FANC-J (=BACH1/BRIP1), FANC-L, FANC-M, FANC-N(=PALB2)	XPF-ERCC1

protection from DNA damage generated by ROS. Furthermore, reports on the interaction between repair pathways also suggest that if one repair process is deficient this function may at least only partially be taken over by the remaining proficient pathways (*table 1*).

Conclusion

Our DNA is constantly exposed to endogenous and exogenous sources of damage. The resulting damage can vary from only single nucleotides to breaks of a single or both DNA strands and repair of the various types of damage is performed by different repair mechanisms. Damage to single nucleotides or bases is repaired by NER, BER or MMR. Interstrand crosslinks are repaired by the ICLR and DSB repair can be performed via HR or NHEJ.
These repair mechanisms all depend on intact proteins. Mutations in genes of these highly conserved pathways are either lethal or lead to rare and mostly severe diseases. These diseases have in common an increased risk of cancer or a prematurely aged phenotype and the phenotypes of these diseases can often be explained by the underlying molecular defects. On the other hand, some of the proteins of repair pathways have been found to interact with other repair pathways, showing that there is a whole network of repair systems. This not only shows that repair mechanisms do cross-react across separate repair pathways, but also that newly elucidated functional interactions may help to understand symptoms which were not entirely explained by a single defect in one repair mechanism alone. It is highly conceivable that future research will report a multitude of these hitherto undescribed interactions. ■

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