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# Variants and Polymorphisms of DNA Repair Genes and Neurodegenerative Diseases

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## 1. Introduction

Oxidative DNA damage is one of the earliest detectable events in several neurodegenerative diseases, often preceding the onset of the clinical symptoms. Moreover, neurons in the adult human brain can re-enter the cell division cycle, likely allowing DNA repair. Impairments of DNA repair pathways are reported in neurons of patients suffering from one of several neurodegenative diseases and might result in the accumulation of mutations critical for neurodegeneration. Current investigation aims at understanding the causes of such impairment (Coppedè & Migliore, 2010). One of the most robust set of data that demonstrates association between DNA repair and neurodegenerative diseases comes from studies on early onset ataxia with ocular motor apraxia and hypoalbuminemia/ataxia with oculomotor apraxia type 1 (EAOH/AOA1), an autosomal recessive form of cerebellar ataxia caused by mutations in the aprataxin (*APTX*) gene. It was shown that aprataxin participates in DNA repair suggesting that genes involved in DNA repair pathways might have a role in neurodegeneration (Hirano et al., 2007; Takahashi et al., 2007). Also parkin, encoded by one of the causative genes of Parkinson's disease (PD), seems to contribute to DNA repair (Kao, 2009). Variants and polymorphisms of DNA repair genes, particularly DNA base excision repair (BER) genes, have been investigated as possible risk factors for Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis (ALS), and other neurodegenerative diseases (Coppedè & Migliore, 2010). There is also evidence that BER could contribute to CAG repeat expansion in Huntington's disease (HD) (Kovtun et al., 2007). Most of the genetic association studies have been performed in the last few years and gave often conflicting or inconclusive results, their power was limited by the sample size of case-control groups, gene-gene interactions were missing, and only common polymorphisms have been included with little or no attention paid to rare gene variants (Coppedè, 2011). In this chapter I discuss the current knowledge on DNA repair gene variants and polymorphisms and major neurodegenerative disorders.

## 2. DNA repair pathways

A brief overview of the major DNA repair pathways in mammals is shown in Table 1. It is estimated that our cells are subjected to a daily average of about one million lesions that, if not properly repaired, can drive mutagenesis, disrupt normal gene expression or create aberrant protein products. Cells have therefore developed several repair systems that can be

generally divided into single stand break (SSB) and double strand break (DSB) repair pathways (Table 1).

| Pathway | Type of repair | Type of damage |
|---|---|---|
| Base excision repair (BER) | SSB | Modifications of DNA bases due to oxidation, alkylation, and deamination |
| Nucleotide excision repair (NER) | SSB | Repair of UV photoproducts, DNA crosslinks, and bulky lesions. |
| Mismatch repair (MMR) | SSB | Repair of mismatches and small insertions or deletions during replication. |
| Homologous recombination (HR) | DSB | Repair of DNA DSBs, such as those caused by ionizing radiations, through recombination with regions of homology (usually a sister chromatid) during late S or G2 phases of the cell cycle |
| Non homologous end joining (NHEJ) | DSB | Repair of DNA DSBs, such as those induced by radiations, without recombination with regions of homology; it occurs during G0, G1, and early S phases of the cell cycle |

Table 1. Major DNA repair pathways in mammalian cells

### 2.1 Base excision repair (BER)

The DNA base excision repair pathway deserves a detailed description since it is believed to be the major pathway for repairing DNA base modifications caused by oxidation, deamination and alkylation. DNA glycosylases catalyze the first step in the BER process by cleaving the N-glycosylic bond between a damaged base and the sugar moiety; after the cleavage the damaged base is released resulting in the formation of an abasic site which is then cleaved by an AP lyase activity or by the major mammalian apurinic/apyrimidinic endonuclease (APEX1). Repair can then proceed through short or long-patch BER. In short-patch BER, which is the most common sub-pathway, a single nucleotide is incorporated into the gap by DNA polymerase β (Pol β) and ligated by the DNA ligase III/ X-ray repair cross-complementing group 1 (XRCC1) complex. In long-patch BER several nucleotides (two to seven-eight) are incorporated, followed by cleavage of the resulting 5′ flap structure and ligation. It has been suggested that after Pol β adds the first nucleotide into the gap, it is substituted by Pol δ/ε which continues long-patch BER. DNA ligase I completes the long-patch pathway. Several other proteins, including the proliferating cell nuclear antigen (PCNA), the RPA protein, and the 5′-flap endonuclease (FEN-1) participate in long-patch BER. Recent evidence suggests that XRCC1 acts as a scaffold protein in short-patch BER, regulating and coordinating the whole process. XRCC1 recruits DNA Pol β and DNA ligase III required for filling and sealing the damaged strand. Moreover, it also interacts with DNA glycosylases and APEX1, mediating their exchange at the damaged site. XRCC1 also interacts with PARP-1, which is one of the cellular sensors of DNA SSBs and DSBs. BER

takes places either in nuclei and mitochondria, and mitochondria have independent BER machinery encoded by nuclear genes. Indeed, several BER enzymes have been identified which have both nuclear and mitochondrial forms. The gaps generated by the action of AP endonucleases/lyases are filled in by Pol γ in the mitochondria, and ligation is mediate by ligase III. To date, there is no evidence of long-patch BER in mitochondria (Weissman et al., 2007).

### 2.2 Nucleotide excision repair (NER)

The nucleotide excision repair pathway (NER) is required for the removal of a wide variety of forms of DNA damage, including UV induced photoproducts, DNA crosslinks, and other bulky lesions. NER involves at least 20-30 proteins or complexes of proteins, and is divided into global genome repair (GGR) and transcription coupled repair (TCR). The two pathways mainly differ in the initial steps that recognize the DNA lesion, and different initial recognition factors are involved. NER senses the presence of a lesion through the distortion it causes to the DNA structure. In GGR DNA damage recognition requires the xeroderma pigmentosum (XP) complementing protein XPC-HR23B-centrin complex. The DNA damage is verified by opening of the DNA strands surrounding the lesion by the transcription factor TFIIH. This is followed by recruitment of XPA and other components of the transcription factor TFIIH to the lesion site. In TCR the recognition step is initiated when a RNA polymerase stalls at a lesion site and requires the Cockayne's syndrome proteins CSA and CSB. After a correct assembly of the NER complex, a fragment of 24-32 nucleotides is incised and removed from the damaged strand by the simultaneous action of the DNA excision repair cross complementing (ERCC) proteins ERCC5 (XPG; 3′ endonuclease) and ERCC4 (XPF; 5′ endonuclease) complexed with ERCC1. Repair is completed by new DNA synthesis mediated by DNA Pol δ/ε, DNA Pol κ, and ligation (DNA ligase I, DNA ligase III) of the nascent DNA to the parental strands using the undamaged strand as a template. The GGR pathway removes damages overall in the genome irrespective of genome location and point in the cell cycle, whereas TCR is required for the specific repair of bulky lesions in the transcribed strand of active genes. Mitochondria have been shown to lack NER, which operates in the nucleus removing the majority of DNA lesions (Fleck & Nielsen, 2004; Subba Rao, 2007).

### 2.3 Mismatch repair (MMR)

Mismatch repair (MMR) corrects mismatches and small insertions or deletions during DNA replication, thus eliminating potentially pre-mutagenic bases. Repair involves recognition of the mismatch by MutSα (MSH2 and MSH6 proteins), or by MutSβ (MSH2 and MSH3 proteins) in the case of small insertions/deletions (1-10 nucleotides). MutLα (a heterodimer of MLH1 and PMS2 proteins) is then recruited and serves to coordinate the process that involves, among others, the PCNA protein for strand discrimination and exonuclease 1, DNA Pol δ and a DNA ligase, for DNA repair (Kunkel & Erie, 2005).

### 2.4 Homologous recombination (HR) and non homologous end joining (NHEJ)

Non homologous end joining (NHEJ) is the major pathway for the repair of DSBs because it can function throughout the cell cycle and does not require a homologous chromosome. Rather, NHEJ involves rejoining of what remains of the two DNA ends, tolerating nucleotide loss or addition at the rejoining site. When a DSB occurs during G0, G1, and early

S phase, the Ku heterodimer (Ku70/Ku80) recognizes DSB ends, aligns them, protects them from excessive degradation, and ultimately prepares them for ligation. The Ku heterodimer is capable of interacting with the nuclease (Artemis-DNA-PKcs) complex, the polymerases (μ and λ), and the ligase (XLF-XRCC4-DNA ligase IV) complex. If complementary ends are not present at the break, the Artemis-DNA-PKcs complex resects some of the overhangs to create single-strand overhangs with short stretches of micro-homology. When necessary, polymerization of missing nucleotides is performed by DNA polymerases. Then, the XLF-XRCC4-LigaseIV complex seals the DSB. When homologous recombination (HR) is used for repair, it is promoted by the recombinase RAD51, the human homolog of the *E. coli* RecA protein, which binds to 3′-tailed single strands at the end of DSBs in a helical fashion and promotes pairing with homologous DNA sequences (usually the sister chromatid) as a prelude to strand invasion and repair of the DSBs. Strand invasion is the invasion of the 3′ end of the single-stranded DNA overhang into the region of complementarity in the intact sister chromatid. The process is directed by RAD51 which forms a nucleoprotein filament that directs homology search, strand pairing, and invasion of the homologous chromosome. Rad51 is assisted in this process by several RAD family members (RAD51B, RAD51C, RAD51D, XRCC2, XRCC3, RAD54, and RAD52). During strand invasion, RAD51 creates a four-stranded Holliday junction intermediate. Then, the invading strand is extended by DNA polymerase η and the Holliday junction is resolved by a RAD51C and XRCC3 directed mechanism. Several nucleases and helicases, such as the RecQ family members, also participate in resolving Holliday junctions. Since eukaryotic genomes contain dispersed repeated DNA, repair of DSBs by HR can occur not only through an interaction with the sister chromatid or the homolog chromosome, but also with repeats on non-homolog chromosomes. Numerous factors affect the decision to repair a DSB via these pathways, and accumulating evidence suggests these major repair pathways both cooperate and compete with each other at double-strand break sites to facilitate efficient repair and promote genomic integrity (Kass & Jasin, 2010).

## 3. Polymorphisms of DNA repair genes and Alzheimer's disease

Alzheimer's disease is a complex multi-factorial neurodegenerative disorder and represents the most common form of dementia in the elderly. In 2006, the worldwide prevalence of AD was 26.6 million. It has been estimated that following the global aging of the world's population this number will quadruple by 2050, suggesting that 1 in 85 persons worldwide will be living with the disease, which is clinically characterized by a progressive neurodegeneration in selected brain regions, including the temporal and parietal lobes and restricted regions within the frontal cortex and the cingulate gyrus, resulting in gross atrophy of the affected regions and leading to memory loss accompanied by changes of behaviour and personality severe enough to affect work, lifelong hobbies or social life (Brookmeyer et al., 2007). Increasing evidence reports oxidative DNA damage in affected brain regions of AD patients, paralleled by a decrease in DNA repair activities, particularly concerning the BER pathway (Lovell et al., 2000; Weissman et al., 2007). This has driven current research to focus on common polymorphisms of BER genes as candidate AD risk factors. Studied genes are those encoding for 8-oxoguanine DNA glycosylase (OGG1), APEX1 and XRCC1. Particularly, we screened 178 Italian late onset AD patients and 146 matched controls for the presence of the *OGG1* Ser326Cys gene polymorphism (rs1052133), observing no difference in allele

and genotype frequencies between patients and controls (Coppedè et al., 2007a). Subsequently, 91 sporadic Turkish AD patients and 93 matched controls have been genotyped for the presence of *OGG1* Ser326Cys, *APEX1* Asp148Glu (rs1130409), *XRCC1* Arg280His (rs25489) and *XRCC1* Arg399Gln (rs25487) polymorphisms, but none of them was associated with increased AD risk (Parildar-Karpuzoğlu et al. 2008). Also a small case-control study performed in Poland with 41 AD patients and 51 controls failed to find significant differences in *OGG1* Ser326Cys allele frequencies between groups (Dorszewska et al., 2009). A borderline association with AD risk ($P$ =0.06) was observed for the *XRCC1* Arg194Trp (rs1799782) polymorphism in a group of 98 Turkish AD patients and 95 healthy subjects (Doğru-Abbasoğlu et al., 2007), but a recent study failed to replicate this association in a larger case-control group of over 200 Chinese AD patients (Quian et al., 2010). Overall, five common functional polymorphisms of BER genes have been investigated as possible AD risk factors, but none of them resulted significantly associated with increased AD risk (Table 2). Also polymorphisms of NER genes have been evaluated as candidate AD risk factors. Particularly, two common polymorphisms of the *XPD (ERCC2)* gene (namely, rs238406 and rs13181), and a silent mutation in exon 11 (T>C at codon 824) of the *XPF (XRCC4)* gene have been investigated in 97 Turkish AD patients and in 101 matched controls, but none of them resulted to be associated with AD risk (Doğru-Abbasoğlu et al., 2006). Poly-ADP-ribose polymerase-1 (PARP-1) is a zinc-finger DNA binding protein that is activated by DNA SSBs or DSBs. The primary function of PARP-1 is in DNA repair processes through the detection of DNA damage and the prevention of chromatide exchanges. PARP-1 poly-ADP-ribosylates several proteins involved in DNA repair including histones, thus inducing local relaxation of the chromatin structure and facilitating the access of repair proteins to damaged DNA. There is evidence for widespread DNA SSBs and DSBs in AD brains, as well as increased PARP-1 activity (Love et al., 1999). Two independent groups evaluated *PARP-1* gene polymorphisms as putative AD risk factors. Infante and coworkers screened 263 Spanish AD patients and 293 matched controls for the presence of two *PARP-1* promoter polymorphisms (–410 and –1672). If evaluated independently, nor *PARP-1* –410 neither *PARP-1* –1672 resulted associated with increased AD risk (Table 2). However, *PARP-1* –410 and *PARP-1* –1672 polymorphisms resulted in linkage disequilibrium and some haplotypes were associated with increased AD risk. Particularly, haplotypes 2-1 and 1-2 were significantly overrepresented in AD individuals and associated with an increased risk for the disease with an adjusted OR of 1.42 and 5.38, respectively (Infante et al., 2007). More recently two *PARP-1* exonic polymorphisms, 414C>T (rs1805404) and 2456T>C (rs1136410), have been evaluated in 120 Chinese AD patients and 111 matched controls (Liu et al., 2010). Again, none of the polymorphisms resulted independently associated with increased AD risk (Table 2). However, authors found that the distributions of haplotype 3-TT and haplotype 4-CC were significantly associated with an increased risk of AD, whereas the haplotype 1-TC showed a protective effect, with OR of 12.2 and 0.52, respectively (Liu et al., 2010). Overall, both studies support the hypothesis that *PARP1* haplotypes might affect AD risk.

### 3.1 Searching for BER gene variants in DNA extracted from post-mortem AD brain

Mao and colleagues extracted nuclear DNA from post-mortem brain specimens of 14 late stage AD patients and 10 neurologically healthy controls. They identified and characterized novel *OGG1* mutations (a single base deletion C796del, and two base substitutions leading

| Reference | Polymorphism | Number of subjects AD/Controls | Variant allele frequency AD/Controls | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Coppedè et al., 2007a | OGG1 Ser326Cys | 178/146 | 0.19/0.18 | 1.04 (0.70-1.55) |
| Parildar-Karpuzoğlu et al. 2008 | OGG1 Ser326Cys | 91/93 | 0.29/0.23 | 1.32 (0.83-2.11) |
| Dorszewska et al., 2009 | OGG1 Ser326Cys | 41/51 | 0.29/0.21 | 1.60 (0.81-3.14) |
| Parildar-Karpuzoğlu et al. 2008 | APEX1 Asp148Glu | 91/93 | 0.33/0.31 | 1.08 (0.70-1.68) |
| Parildar-Karpuzoğlu et al. 2008 | XRCC1 Arg280His | 91/93 | 0.06/0.10 | 0.53 (0.24-1.14) |
| Parildar-Karpuzoğlu et al. 2008 | XRCC1 Arg399Gln | 91/93 | 034/0.33 | 1.05 (0.68-1.63) |
| Doğru-Abbasoğlu et al., 2007 | XRCC1 Arg194Trp | 98/95 | 0.11/0.06 | 2.06 (0.97-4.37) |
| Quian et al., 2010 | XRCC1 Arg194Trp | 212/203 | 0.31/0.31 | 1.04 (0.70-1.52) |
| Doğru-Abbasoğlu et al., 2006 | ERCC2 rs238406 (XPD exon 6) | 97/101 | 0.40/0.42 | 0.94 (0.63-1.41) |
| Doğru-Abbasoğlu et al., 2006 | ERCC2 rs13181 (XPD exon 23) | 97/101 | 0.41/0.36 | 1.24 (0.83-1.86) |
| Doğru-Abbasoğlu et al., 2006 | ERCC4 (XPF exon 11) | 97/101 | 0.37/0.35 | 1.09 (0.72-1.64) |
| Infante et al., 2007a | PARP-1 (-410) | 263/293 | 0.35/0.33 | 1.08 (0.84-1.38) |
| Infante et al., 2007a | PARP-1 (-1672) | 263/293 | 0.17/0.18 | 0.94 (0.69-1.27) |
| Liu et al., 2010 | PARP-1 (rs1805404) | 120/111 | 0.53/0.59 | 0.76 (0.53-1.11) |
| Liu et al., 2010 | PARP-1 (rs1136410) | 120/111 | 0.52/0.59 | 0.75 (0.52-1.09) |

Table 2. DNA repair gene polymorphisms and risk of Alzheimer's disease

to Ala53Thr or Ala288Val amino acidic changes, respectively) in 4 of 14 AD subjects. Particularly, two AD patients carried the C796 deletion, one patient had the Ala53Thr substitution, and another patient carried the Ala288Val substitution. No mutations were found in any of 10 studied age-matched controls (Mao et al., 2007). This study is not an

association study for risk assessment but a genetic screening performed on brain DNA specimens searching for novel *OGG1* variants. The authors created the mutant proteins by site-directed mutagenesis observing that the C796del mutant OGG1 lacks glycosylase activity, whereas both Ala53Thr and Ala288Val substitutions result in 40–50% reduced activity (Mao et al., 2007). Therefore, we cannot exclude that the activity of the OGG1 protein might be partially impaired by rare gene variants in some AD subjects. However, given the limited sample-size of the studied case-control group, further studies are required to confirm this hypothesis.

## 4. Polymorphisms of DNA repair genes and amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is one of the major neurodegenerative diseases alongside AD and PD. It is a progressive disorder characterized by the degeneration of motor neurons of the motor cortex, brainstem and spinal cord. The incidence of the disease is similar worldwide and ranges from 1 to 3 cases per 100,000 individuals per year, with the exception of some high-risk areas around the Pacific Rim. Several studies report increased oxidative DNA damage and a compromised DNA repair activity, particularly BER activity, in spinal cords and other tissues of ALS patients (Bogdanov et al., 2000; Ferrante et al., 1997; Kikuchi et al., 2002; Kisby et al., 1997). Missense mutations in the gene encoding *APEX1* were found in DNA obtained from 8 of 11 ALS patients, including the common *APEX1* Asp148Glu polymorphism (Hayward et al., 1999), that was subsequently associated with increased ALS risk in a Scottish cohort of 117 ALS patients and 58 controls, and in an Irish group of 105 ALS individuals and 82 controls (Greenway et al., 2004). The analysis of 88 English ALS patients and 88 matched controls still revealed an increased frequency of the variant allele in the ALS cohort, even if not statistically significant (Tomkins et al. 2000). We have recently performed the largest case-control study aimed at clarifying the role of *APEX1* Asp148Glu in sporadic ALS pathogenesis. No difference in *APEX1* Asp148Glu allele and genotype frequencies was found between 134 ALS patients and 129 controls of Italian origin, nor was the polymorphism associated with disease age or site of onset, or duration of the disease, suggesting that it might not play a major role in ALS pathogenesis in the Italian population (Coppedè et al., 2010a). The ALSGene database (www.alsgene.org) is a public database containing all the ALS genetic association studies, genome-wide association studies and updated meta-analyses of the literature. A meta-analysis of the four studies described above revealed a significant increased frequency of the variant 148Glu allele in ALS cases with respect to controls, suggesting a protective role for the wild type 148Asp variant with an OR = 0.78 (95%CI=0.62-0.97) (www.alsgene.org). Our analysis of the *OGG1* Ser326Cys polymorphism in 136 ALS patients and 129 matched controls of Italian origin revealed a significant association of the variant allele with increased ALS risk (Coppedè et al., 2007b) (Table 3). At best of our knowledge this study is the first in the literature addressing this issue, still pending replication in other populations. More recently, we screened over 400 individuals, including 206 ALS patients and 203 matched controls of Italian origin for the presence of *XRCC1* Arg194Trp, Arg280His and Arg399Gln polymorphisms, observing a significant increased frequency of the 399Gln variant allele and a borderline significant decreased frequency of the 194Trp allele in ALS patients with respect to controls (Coppedè et al., 2010b). Interestingly, others have evaluated the same *XRCC1* polymorphisms and two

additional ones (rs939461 and rs915927) in 108 ALS patients and 39 controls from New-England, observing that rs939461 was associated with reduced ALS risk, and Arg399Gln with a borderline significant reduced risk (Fang et al., 2010) (Table 3). Overall, even if still inconclusive, the results of both studies suggest that additional investigation is required to clarify the role of *XRCC1* polymorphisms and haplotypes in ALS pathogenesis.

### 4.1 Less frequent BER gene variants and polymorphisms

Alongside with common BER gene polymorphisms, less frequent gene variants or polymorphisms have been observed in the DNA of both ALS subjects and matched controls, but with very low allele frequencies and no significant difference between groups. Some examples are *APEX1* 1835C/A (Intron3), *APEX1* 2712A/T (3'UTR), *APEX1* 459C/T (Exon1), and *APEX1* rs1048945 (Q51H) (Hayward et al., 1999; Tomkins et al., 2000).

| Reference | Polymorphism | Number of subjects ALS/Controls | Variant allele frequency ALS/Controls | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Coppedè et al., 2007b | OGG1 Ser326Cys | 136/129 | 0.26/0.18 | 1.62 (1.07-2.45) |
| Hayward et al. 1999 | APEX1 Asp148Glu | 117/58 | 0.62/0.49 | 1.66 (1.06-2.60) |
| Tomkins et al. 2000 | APEX1 Asp148Glu | 88/88 | 0.51/0.45 | 1.28 (0.85-1.95) |
| Greenway et al. 2004 | APEX1 Asp148Glu | 105/82 | 0.60/0.51 | 1.46 (0.97-2.21) |
| Coppedè et al. 2010a | APEX1 Asp148Glu | 134/129 | 0.44/0.45 | 0.99 (0.70-1.40) |
| Coppedè et al. 2010b | XRCC1 Arg194Trp | 206/195 | 0.05/0.08 | 0.58 (0.32-1.05) |
| Coppedè et al. 2010b | XRCC1 Arg280His | 205/203 | 0.09/0.08 | 1.25 (0.76-2.04) |
| Coppedè et al. 2010b | XRCC1 Arg399Gln | 197/194 | 0.39/0.28 | 1.39 (1.05-1.85) |
| Fang et al. 2010 | XRCC1 Arg194Trp | 108/39 | 0.06/0.03 | 2.4 (0.5-2.2)[a] |
| Fang et al. 2010 | XRCC1 Arg280His | 108/39 | 0.05/0.03 | 2.0 (0.4-2.0)[a] |
| Fang et al. 2010 | XRCC1 Arg399Gln | 108/39 | 0.35/0.47 | 0.4 (0.2-1.0)[a] |
| Fang et al. 2010 | XRCC1 rs915927 | 108/39 | 0.45/0.33 | 2.4 (0.5-2.2)[a] |
| Fang et al. 2010 | XRCC1 rs939461 | 108/39 | 0.06/0.15 | 0.4 (0.1-0.9)[a] |

Table 3. DNA repair gene polymorphisms and risk of Amyotrophic Lateral sclerosis[a] OR are derived from the original paper and referred to (heterozygous+minor homozygous) vs major homozygous.

## 5. Polymorphisms of DNA repair genes and Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder after AD, affecting 1–2% of the population over the age of 50 years, and is characterized by progressive and profound loss of neuromelanin containing dopaminergic neurons in the *substantia nigra* (SN) resulting in resting tremor, rigidity, bradykinesia, and postural instability. The majority of PD cases are sporadic idiopathic forms, resulting from three interactive events: an individual's inherited genetic susceptibility, subsequent exposure to environmental risk factors, and aging (Bekris et al., 2010). However, in a minority of the cases PD is inherited as a Mendelian trait. Parkin is an E3 ubiquitin ligase that acts on a variety of substrates, resulting in polyubiquitination and degradation by the proteasome or monoubiquitination and regulation of biological activity. Mutation of *parkin* is one of the most prevalent causes of autosomal recessive familial PD and a recent study has shown that parkin is essential for optimal repair of DNA damage. Particularly, DNA damage induces nuclear translocation of parkin leading to interactions with PCNA and possibly other nuclear proteins involved in DNA repair (Kao, 2009). Moreover, parkin protects mitochondrial genome integrity and supports mitochondrial DNA (mtDNA) repair (Rothfuss et al., 2009). DNA polymerase gamma (POLG1) participates in mtDNA replication and repair, thus playing a fundamental role in mtDNA maintenance. Missense mutations in *POLG1* co-segregate with a phenotype that includes progressive external ophthalmoplegia and parkinsonism (Hudson et al., 2007). Moreover, missense mutations in *POLG1* have been reported in case studies, in which parkinsonism was part of the clinical symptoms (Davidzon et al., 2006; Remes et al., 2008). *POLG1* mutations and polymorphisms have been also investigated in sporadic idiopathic PD, among them a polyglutamine (poly-Q) located in the *N*-terminal of POLG1, encoded by a CAG repeat in exon 2. The poly-Q tract normally consists of 10Q (frequency >80%), followed by 11Q (frequency > 6-12%), whereas non-10Q/11Q alleles are considered as less frequent alleles. Several authors investigated whether or not non-10Q alleles are more frequent in PD cases than in matched controls (Hudson et al., 2009; Luoma et al., 2007; Taanman & Shapira, 2005; Tiangyou et al., 2006). Eerola and coworkers recently screened 641 PD patients and 292 controls from USA and performed a pooled analysis of their data with those available in the literature (Hudson et al., 2009; Luoma et al., 2007; Taanman & Shapira, 2005; Tiangyou et al., 2006) for a total of 1163 sporadic PD patients and 1214 controls observing that variant alleles defined as non-10Q were significantly increased in PD patients than in controls (16.3%vs.13.4%, $p = 0.005$) (Eerola et al., 2010). A few months later Anvret and coworkers screened 243 PD patients and 279 matched controls from Sweden, observing that non10Q/11Q alleles were more frequent in PD cases than in controls with an OR of 2.0 (1.3-3.1, 95%CI) strengthening the evidence that non frequent *POLG1* alleles might be more frequent in sporadic PD patients than in controls, thus representing a PD risk factor (Anvret et al., 2010) (Table 4). We screened 139 sporadic PD patients and 211 healthy matched controls for the presence of the *OGG1* Ser326Cys polymorphism. The Cys326 allele frequency was similar between the groups (0.20 in PD patients and 0.19 in controls), and no difference in genotype frequencies was observed. Moreover, the *OGG1* Ser326Cys polymorphism was not associated with PD age at onset (Coppedè et al., 2010c). In human cells the oxidized purine nucleoside triphosphatase MTH1 efficiently hydrolyzes oxidized purines such as 8-oxo-guanine in the nucleotide pools, thus avoiding their incorporation into DNA or RNA. A Val83Met polymorphism of the *MTH1* gene was studied in 73

Japanese patients with sporadic PD and 151 age-matched controls but was not associated with sporadic PD risk (Satoh & Kuroda, 2000). Another *MTH1* polymorphism (Ile45Thr) was investigated in 106 PD patients and 135 unrelated controls from China. The variant allele frequency resulted borderline increased in PD males (Jiang et al., 2008). This finding is pending replication in other populations. *PARP1* promoter polymorphisms (-410C/T, -1672G/A, and a (CA)n microsatellite) have been investigated in 146 Spanish PD cases and 161 matched controls. A protective effect against PD was found for heterozygosity at -410 (OR = 0.44) and (CA)n microsatellite (OR = 0.53) polymorphisms, and heterozygosity at -1672 polymorphism delayed by 4 years on the onset age of PD (Infante et al., 2007). Also these findings are original and waiting for replication in additional case-control groups (Table 4).

| Reference | Polymorphism | Number of subjects PD/Controls | Variant allele frequency PD/Controls | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Eerola et al., 2010 | POLG1 Poly-Q tract | 641/292 | 0.17/0.12 | OR = n.a. *P* = 0.004 |
| Eerola et al., 2010 | POLG1 Poly-Q tract | 1163/1214[a] | 0.16/0.13 | OR = n.a. *P* = 0.005 |
| Anvret et al., 2010 | POLG1 Poly-Q tract | 243/279 | 0.11/0.06 | 2.0 (1.3-3.1) |
| Coppedè et al., 2010c | OGG1 Ser326Cys | 139/211 | 0.20/0.19 | 1.05 (0.72-1.53) |
| Satoh & Kuroda, 2000 | MTH1 Val83Met | 73/151 | 0.07/0.11 | OR = n.a. *P* = 0.219 |
| Jiang et al., 2008 | MTH1 Ile45Thr | 106/135 | 0.05/0.02 | OR = n.a. *P* = 0.08[b] |
| Infante et al., 2007b | PARP-1 (-410) | 146/161 | 0.35/0.53[c] | 0.44 (0.26-0.75) |
| Infante et al., 2007b | PARP-1 (-1672)[d] | 146/161 | 0.29/0.27[c] | 0.87 (0.50-1.52) |
| Infante et al., 2007b | PARP-1 (CA)n | 146/161 | 0.36/0.50[c] | 0.53 (0.31-0.90) |

Table 4. DNA repair gene polymorphisms and risk of Parkinson's disease. [a] = pooled-analysis of (Eerola et al., 2010, Hudson et al., 2009; Luoma et al., 2007; Taanman & Shapira, 2005; Tiangyou et al., 2006). [b] = Allele frequency difference (PD/Controls) approached significance in the male subgroup (0.07/0.02, *P* = 0.05). [c] = Heterozygous genotype frequency. [d] = Associated with PD age at onset

### 5.1 Other mutations and polymorphisms

As previously observed, several *POLG1* mutations have been observed to co-segregate in families with parkinsonism. For a detailed description I suggest a recent review by Orsucci and coworkers (Orsucci et al., 2010).

## 6. Other neurodegenerative diseases

### 6.1 Spinocerebellar ataxias

Hereditary ataxias are a heterogeneous group of diseases with different patterns of inheritance. Some of them are caused by recessive mutations in genes involved in DNA repair pathways that likely predispose the affected individuals to neurodegeneration. Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) is caused by autosomal recessive mutations in the gene encoding tyrosyl-DNA phosphodiesterase 1 (TDP1), a protein required for the repair of DNA SSBs that arise independent of DNA replication from abortive topoisomerase 1 activity or oxidative stress. Ataxia-telangiectasia (AT), ataxia-telangiectasia-like disorder (ATLD), ataxia oculomotor apraxia type 1 (AOA1) and ataxia oculomotor apraxia type 2A (AOA2) are a subgroup of the autosomal recessive spinocerebellar ataxias characterized by cerebellar atrophy and oculomotor apraxia. The progressive neurodegeneration described in AT and ATLD is due to mutations in genes encoding for ATM and Mre11, respectively. ATM recognizes and signals DNA DSBs to the cell cycle checkpoints and the DNA repair machinery. The Mre11 DNA repair complex, composed of Rad50, Mre11 and Nbs1 proteins, is involved in DNA damage recognition, DNA repair, and initiating cell cycle checkpoints. ATM and the Mre11 complex combine to recognize and signal DNA DSBs. AOA1 is caused by mutations in the gene encoding aprataxin (APTX), a nuclear protein that interacts with several DNA repair proteins, including XRCC1, Polβ, DNA ligase III, PARP-1, and p53. It functions in the endprocessing of DNA SSBs removing 3′-phosphate, 5′-phosphate, and 3′-phosphoglycolate ends. AOA2 is caused by autosomal recessive mutations in the gene encoding senataxin (SETX). SETX is a member of the superfamily I DNA/RNA helicases, likely involved in oxidative DNA damage response. *SETX* mutations have been also linked to juvenile ALS. Overall, spinocerebellar ataxias deficient in DNA damage responses represent the most robust set of data linking mutations in DNA repair genes to neurodegeneration (Gueven et al., 2007; Martin, 2008).

### 6.2 Huntington's disease

Huntington's disease (HD) is a progressive neurodegenerative disorder resulting in cognitive impairment, choreiform movements and death which usually occurs 15–20 years after the onset of the symptoms. The disease is also characterized by psychiatric and behavioural disturbances. HD is an autosomal dominant disorder caused by a CAG repeat expansion within exon 1 of the gene encoding for huntingtin (*IT15*) on chromosome 4. In the normal population the number of CAG repeats is maintained below 35, while in individuals affected by HD it ranges from 35 to more than 100, resulting in an expanded polyglutamine segment in the protein. Age at onset of the disease is inversely correlated with the CAG repeat length; moreover the length of the expanded polyglutamine segment seems to be related to the rate of clinical progression of neurological symptoms and to the progression of motor impairment, but not to psychiatric symptoms. Somatic CAG repeat expansion in the gene encoding for huntingtin has been observed in several HD tissues, including the striatum which is the region most affected by the disease and the OGG1 protein has been involved in somatic CAG repeat expansion in HD, suggesting that it might contribute to disease age at onset (Kovtun et al. 2007). We recently observed a weak borderline association between the *OGG1* Ser326Cys polymorphism and HD age at onset in a small group of 91 HD subjects (Coppedè et al. 2010d). However, replication of the study in a

cohort of more than 400 HD individuals failed to confirm the association between *OGG1* Ser326Cys and HD age at onset (Taherzadeh-Fard et al., 2010).

### 6.3 Multiple sclerosis

Multiple sclerosis (MS) has been classically regarded as an inflammatory demyelinating disease of the central nervous system. In recent years, it is also becoming increasingly apparent that there is a significant neurodegenerative component in the disease (Moore, 2010). MS is a complex autoimmune disease with a prominent genetic component. The primary genetic risk factor is the human leukocyte antigen *(HLA)-DRB1*1501* allele; however, much of the remaining genetic contribution to MS remains to be elucidated. Briggs and collaborators screened 1,343 MS cases and 1,379 healthy controls of European ancestry for a total of 485 single nucleotide polymorphisms within 72 genes related to DNA repair pathways. Only a single nucleotide polymorphism (rs1264307) within the general transcription factor IIH polypeptide 4 gene (*GTF2H4*), a nucleotide excision repair gene, was significantly associated with MS risk (OR = 0.7) after correcting for multiple testing. However, using a nonparametric approach comprising the Random Forests and CART algorithms, authors observed evidence for a predictive relation for MS based on 9 variants in nucleotide excision repair (rs4134860, rs2974754, rs7783714, rs4134813, rs2957873 and rs4150454), homologous recombination (rs9562605), and nonhomologous end-joining genes (rs9293329 and rs1231201). Specifically, variants within nucleotide excision repair genes were most prominent among predictors of MS (Briggs et al., 2010). Variants of DNA repair genes, particularly *BRCA2* (rs1801406) and *XRCC5* (rs207906), might also increase the risk for the development of secondary acute promyelocytic leukemia in MS patients (Hasan et al., 2011).

### 6.4 Diseases caused by mutations of NER genes

Xeroderma pigmentosum (XP), Cockayne's syndrome (CS) and trichothiodystropy (TTD) represent a clinically heterogeneous group of progeroid syndromes characterized by defects in NER proteins. A subset of these patients exhibits neurological dysfunction and neurodegeneration, and many XP patients have high cancer predisposition, thus linking DNA repair defects to premature aging, cancer and neurodegeneration. Several studies performed in mice, as well as in cell cultures, suggest that neurodegeneration in XP and CS patients might arise as a consequence of impaired repair of oxidative DNA lesions caused by mutations of NER genes. Details are provided in our recent updated review (Coppedè & Migliore, 2010)

## 7. Conclusions

The present chapter describes the current knowledge concerning DNA repair genes and neurodegeneration. Studies in ataxias (section 6.1) have undoubtedly linked genes involved in DNA repair to neurodegeneration. These observations, alongside with evidence of increased DNA damage in affected brain regions, have driven researchers to search for variant and polymorphisms of DNA repair genes in major neurodegenerative diseases such as AD, ALS and PD. Studies in sporadic late onset AD patients (Section 3) suggest that common polymorphisms of BER genes, namely *OGG1* Ser326Cys, *APEX1* Asp148Glu, and *XRCC1* (Arg194Trp, Arg280His and Arg399Gln) are unlikely to represent major AD risk factors. However, further studies are required to replicate and clarify the associations observed between *PARP-1* haplotypes and disease risk. Moreover, the power of these studies was limited by the sample size of case-control groups (Table 2), gene-gene

interactions were missing, and only common polymorphisms have been included with little or no attention paid to rare gene variants. Concerning ALS, although results are still inconclusive, some studies performed in northern Europe suggest a possible association between the *APEX1* Asp148Glu polymorphism and disease risk, the *OGG1* Ser326Cys polymorphism was associated with increased ALS risk in Italy, and *XRCC1* variants gave conflicting results in different populations (Table 3). Overall, these studies (Section 4) suggest the need of further investigation aimed at addressing the contribution of haplotypes, gene-gene and gene-environment interactions. There is evidence for a contribution of *POLG1* mutations in PD, and parkin seems to be involved in mtDNA repair, thus strengthening the contribution of mtDNA mutations to disease pathogenesis (Section 5). Increasing evidence suggests that BER proteins might be involved in CAG repeat expansion in somatic cells of HD individuals (Section 6.2), however studies aimed at addressing the possible contribution of variant of BER genes to disease age at onset are still in their beginnings. Recent evidence also suggests a possible contribution of NER genes in MS (Section 6.3), and the impaired ability to repair oxidative DNA damage might cause neurodegeneration observed in progeroid syndromes caused by mutations of NER genes (Section 6.4). In summary, increasing evidence supports a role for DNA repair genes in neurodegeneration, making this field a promising area for further investigation.

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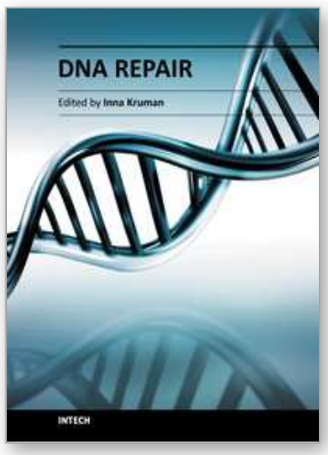


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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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