Gene Section
Review

XRCC2 (X-ray repair cross complementing 2)

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Abstract

XRCC2 is one of five somatic RAD51 paralogs, all of which have Walker A and B ATPase motifs. Each of the paralogs, including XRCC2, has a function in DNA double-strand break repair by homologous recombination (HR). However, their individual roles are not as well understood as that of RAD51 itself.

The XRCC2 protein forms a complex (BCDX2) with three other RAD51 paralogs, RAD51B, RAD51C and RAD51D. It is believed that the BCDX2 complex mediates HR downstream of BRCA2 but upstream of RAD51, as XRCC2 is involved in the assembly of RAD51 into DNA damage foci. XRCC2 can bind DNA and, along with RAD51D, can promote homologous pairing in vitro. Consistent with its role in HR, XRCC2-deficient cells have increased levels of spontaneous chromosome instability, and exhibit hypersensitivity to DNA interstrand crosslinking agents such as mitomycin C and cisplatin as well as ionizing radiation, alkylating agents and aldehydes. XRCC2 also functions in promoting DNA replication and chromosome segregation.

Biallelic mutation of XRCC2 (FANCU) causes the FA-U subtype of FA, while heterozygosity for deleterious mutations in XRCC2 may be associated with an increased breast cancer risk. XRCC2 appears to function 'downstream' in the FA pathway, since it is not required for FANCD2 monoubiquitination, which is the central step in the FA pathway.

Clinically, the only known FA-U patient in the world exhibits severe congenital abnormalities, but had not developed, by seven years of age, the bone marrow failure and cancer that are often seen in patients from other FA complementation groups.

Keywords
Fanconi anemia, Breast Cancer Susceptibility, Tumor Suppressor, Homologous Recombination, DNA Repair, RAD51 Paralog

Identity
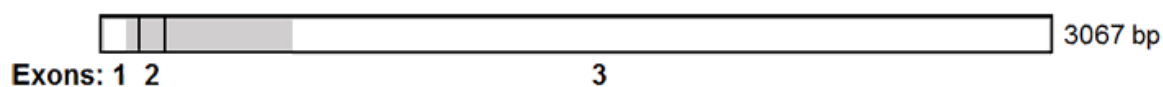
Other names: FANCU

HGNC (Hugo): XRCC2

Location: 7q36.1

Local order
As outlined by NCBI (Gene), coding genes located most proximal to XRCC2 on 16p12.2, in the centromeric to telomeric direction, are GALNTL5 (polypeptide N-acetylgalactosaminyltranserase like 5), GALNT11 (polypeptide N-acetylgalactosaminyltransferase 11), KMT2C (lysine methyltransferase 2C), XRCC2, ACTR3B (ARP3 actin related protein 3 B homolog B), DPP6 (dipeptidyl peptidase like 6), and LOC107984014.

DNA/RNA

In a screen for X-ray sensitive cellular mutants in Chinese hamster ovary (CHO) cells, the irs1 clone, which was thought to be deficient in a novel DNA repair gene, was obtained (Jones et al., 1987).

Exon structure of the human XRCC2 gene. Exons are delineated by a vertical black line. For each exon, coding sequence is shown in grey, while non-coding sequence in exons 1 and 3 is displayed in white.

Two groups subsequently mapped the region containing the defective gene to 7q36.1 in humans based on somatic cell hybrids capable of complementing the hypersensitivity of irs1 cells to the DNA interstrand crosslinking agent mitomycin C (MMC) (Jones et al., 1995; Thacker et al., 1995). The human cDNA was subsequently identified as a novel gene with considerable homology on the protein level to the RAD51 recombinase (Liu et al., 1998). The single protein coding human mRNA transcript (XRCC2-201), with a length of 3067 bp, has three coding exons (for a protein of 280 a.a.) arranged as shown below:

Description

The human XRCC2 gene locus is 29.66 kb in length.

Transcription

The single full-length transcript for human XRCC2 is 3,067 bp and there are no additional confirmed protein coding variants known (http://www.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000196584;r=7:152644779-152676165).

Protein

Note
The five somatic mammalian RAD51 paralogs, RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3, form two prominent paralog-only protein complexes. These are the RAD51B-RAD51C-RAD51D-XRCC2 (**BCDX2**) and RAD51C-XRCC3 (**CX3**) complexes (Liu et al., 2002; Masson et al., 2001). RAD51C, which like XRCC2 is a FA protein, is the only member of both complexes. As demonstrated using a yeast 2-hybrid assay, XRCC2 directly binds RAD51D within the BCDX2 complex (Schild et al., 2000). Further, experiments with purified proteins expressed in insect cells indicate that RAD51D bridges RAD51C and XRCC2 together (Schild et al., 2000). The RNF138 E3 ubiquitin ligase appears to regulate the interaction of RAD51D with XRCC2 by ubiquitinating RAD51D and promoting ubiquitin-mediated degradation of this RAD51 paralog (Yard et al., 2016). XRCC2 itself regulates the abundance of the BCDX2 complex, since the RAD51B, RAD51C and RAD51D proteins display decreased stability in the absence of XRCC2 (Park et al., 2016).

Other proteins, including RAD51 (Rodrigue et al., 2006) and HELQ, directly interact with the assembled BCDX2 complex (Adelman et al., 2013; Takata et al., 2013). It has also been reported that the BLM helicase interacts with the RAD51D-XRCC2 complex via direct binding to RAD51D (Braybrooke et al., 2003).

XRCC2 is essential for normal development in mice, as disruption of the Xrcc2 gene results in embryonic lethality ranging from mid-gestation to birth (Deans et al., 2000).

Description

While each of the five somatic RAD51 paralogs in humans has a somewhat similar size as RAD51, the paralogs show relatively low homology to RAD51. Specifically, the human XRCC2 protein has a size of 34 kD while human RAD51 has a molecular mass of 37 kD; human XRCC2 is 20% identical to human RAD51 at the amino acid level (Liu et al., 1998).

Still, each of the RAD51 paralogs, including XRCC2, shares Walker A and Walker B ATPase motifs with RAD51. The Walker A and Walker B motifs in human XRCC2 are present at a.a. 48-55 and 145-149, respectively (Miller et al., 2004), as shown below. No other functional domains have been identified in XRCC2.
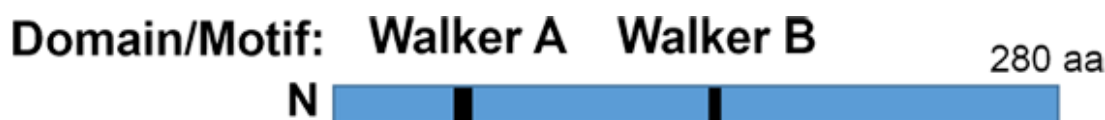
Expression

According to the Human Protein Atlas (online), XRCC2 mRNA is expressed in cell lines representing a variety of tissue types, including the brain, skin, myeloid and lymphoid compartments, lung, breast and kidney.

The transcription factors MYC and ZNF281 bind to the XRCC2 promoter (Luoto et al., 2010; Pieraccioli et al., 2016).

Further, it has been demonstrated that ZNF281 positively regulates XRCC2 expression (Pieraccioli et al., 2016).

Additionally, EZH2, a subunit of the PRC2 transcriptional repressor complex, may have a role in downregulating XRCC2 expression, as increased expression of EZH2 in breast cancer cells is associated with epigenetic repression of XRCC2 and other RAD51 paralogs (Zeidler and Kleer, 2006).

Known functional domains present in XRCC2: the Walker A and B ATPase motifs are diagramed in black.

Localisation

Consistent with its role in DNA repair, XRCC2 is a nuclear protein (O'Regan et al., 2001). When assayed by immunofluorescence microscopy and chromatin immunoprecipitation, XRCC2 localizes to engineered DNA double-strand breaks (DSBs) in nuclei (Rodrigue et al., 2006). RAD51C also colocalizes with γ-H2AX in nuclear foci induced by etoposide (Rodrigue et al., 2006). Aside of its nuclear localization, XRCC2 also localizes to centrosomes within the cytoplasm (Cappelli et al., 2011).

Function

Each of the five somatic RAD51 paralogs, including XRCC2, is required for DNA repair by homologous recombination (HR) (Johnson et al., 1999; Takata et al., 2001). However, the role of XRCC2 and other RAD51 paralogs in promoting HR is less well understood than that of RAD51, which is the main mammalian recombinase. Still, molecular details concerning the role of XRCC2 in HR are emerging. For example, XRCC2 and other RAD51 paralogs appear to act upstream of RAD51 and regulate its assembly into nuclear foci (Chun et al., 2013; Park et al., 2016; Patel et al., 2017; Takata et al., 2001). Further, purified XRCC2 can stimulate the ATPase activity of RAD51, thereby promoting the stability of the RAD51 oligomer and enhancing RAD51-dependent strand exchange during HR (Shim et al., 2004). While it is currently unclear whether this function of XRCC2 occurs within the context of the BCDX2 complex, the presence of XRCC2 favors short-tract gene conversion over long-tract gene conversion (Nagaraju et al., 2009). Interestingly, work in Arabidopsis thaliana has demonstrated the existence of a RAD51-independent single-strand annealing (SSA) mechanism involving XRCC2, RAD51B and RAD51D (Serra et al., 2013); like HR, SSA is also a homology-dependent form of DNA repair. XRCC2 could also play a more direct role in HR than what is described above, since purified XRCC2 and RAD51D can stimulate homologous pairing of single-strand DNA with double-strand DNA in vitro (Kurumizaka et al., 2002).

Additional data suggests that XRCC2 functions in HR in the context of the previously mentioned BCDX2 protein complex. The fact that the BCDX2 complex binds Holliday junctions in vitro (Yokoyama et al., 2004) supports this possibility. BRCA2, which also regulates the assembly of RAD51 foci, appears to be epistatic with the BCDX2 complex in mediating HR (Chun et al., 2013).

The BCDX2 complex also binds to replication forks in vitro (Yokoyama et al., 2004). In support of a function in rescuing stalled or collapsed replication forks, XRCC2-deficient cells display compromised replication fork dynamics (Daboussi et al., 2008). This is consistent with the fact that HR is known to function in promoting the stability and rescue of arrested replication forks (Kolinjivadi et al., 2017).

As a mediator of HR, XRCC2 also suppresses spontaneous chromosome abnormalities including breaks, deletions and translocations (Cui et al., 1999; Takata et al., 2001).

Also, related to its function in HR, XRCC2-deficient cells are hypersensitive to a variety of DNA damaging agents that directly or indirectly yield DNA double-strand breaks, including ionizing radiation, DNA interstrand crosslinking agents such as mitomycin C (MMC) and cisplatin, aldehydes, tirapazamine and temozolomide (Evans et al., 2008; Jones et al., 1987; Park et al., 2016; Roos et al., 2009; Zheng et al., 2012). Another function of XRCC2 that is potentially related to HR is in promoting accurate chromosome segregation and preventing mitotic catastrophe (Cappelli et al., 2011; Daboussi et al., 2005; Griffin et al., 2000). However, it has been reported that XRCC2 localizes to centrosomes and it is possible that polyploidy or aneuploidy observed in XRCC2-deficient cells is associated with supernumerary centrosomes rather than a DNA repair defect (Cappelli et al., 2011; Daboussi et al., 2005; Griffin et al., 2000).

Associated with its function in HR, XRCC2 also plays an essential role in promoting normal development (Deans et al., 2000). This includes a function in promoting normal lymphocyte development (Caddle et al., 2008). Also, XRCC2 promotes survival of proliferating neural precursors in vivo (Orii et al., 2006).

Homology

Based on HomoloGene (NCBI), the following are homologs of the human XRCC2 gene (NP_005422.1, 280 a.a.):
Chimpanzee (Pan troglodytes) XP_001140134.1, 280 a.a.

Rhesus monkey (Macaca mulatta) XP_001108141.1, 280 a.a.
Dog (Canis lupus familiaris) XP_532771.3, 279 a.a.
Cattle (Bos taurus) NP_001095824.1, 280 a.a.
Mouse (Mus musculus) NP_065595.2, 278 a.a.
Rat (Rattus norvegicus) NP_001102685.1, 278 a.a.
Chicken (Gallus gallus) XP_418543.3, 278 a.a.
Tropical Clawed Frog (Xenopus tropicalis) XP_002932541.2, 282 a.a.

Mutations

Note

Generally, germ-line alterations in XRCC2 are quite rare. In the largest study to date, of 13,087 breast cancer and 5,488 control cases from the UK, a total of 11 truncating and 32 rare missense variants were found (Decker et al., 2017). A recent study functionally characterized breast cancer-associated variants and found that each of the truncating or frameshift variants displayed compromised activity, while most of the missense variants tested displayed a minor change or no change in activity (Hilbers et al., 2016). Notably, a bi-allelic germ-line nonsense mutation in XRCC2 c.643C>T encoding p.R215X is causative for the U complementation group of Fanconi anemia, FA-U (Park et al., 2016; Shamseldin et al., 2012).

XRCC2 was initially published as a low-risk breast cancer susceptibility gene, similar to other late FA genes such as BRCA1, BRCA2, PALB2 and RAD51C (Park et al., 2012). However, subsequent studies could not confirm these findings and also presented data that the initial missense classification based on bioinformatic prediction tools was not correct (see below -> Breast Cancer) (Decker et al., 2017; Hilbers et al., 2012; Pelttari et al., 2015).

Epigenetics

Increased levels of the PRC2 subunit, EZH2, leads to epigenetic repression of XRCC2 in breast cancer cells (Zeidler and Kleer, 2006). Additionally, miR-7 interacts with XRCC2 mRNA in colorectal cancer cells; overexpression of miR-7 reduces XRCC2 promoter activity (Xu et al., 2014). Interestingly, XRCC2 promoter activity seems to be highly up-regulated in nearly all types of cancers (Chen et al., 2018).

Implicated in

Fanconi Anemia (FA)

Note

Germ-line bi-allelic and heterozygous mutations of XRCC2 (FANCU) are associated with different outcomes. Bi-allelic inactivating mutation of XRCC2 results in the FA-U subtype, while heterozygous inheritance of pathogenic XRCC2 mutations might increase the lifetime risk of germ-line mutation carriers for developing breast cancer.

Disease

Using whole exome sequencing, bi-allelic mutations in RAD51C were found in a 2.5 year old boy born to healthy Saudi first cousins with a spectrum of severe congenital anomalies suggestive of FA. These included microcephaly, facial palsy, a lack of thumbs, short stature and an ectopic left kidney (Shamseldin et al., 2012). Importantly, bi-allelic loss-of-function mutations were detected in two other genes, MTBP and RGS3, in addition to XRCC2 (Shamseldin et al., 2012). The authors scrutinized these genes with bi-allelic mutations, since this inheritance pattern is typical of FA. XRCC2 emerged as a candidate FA gene, in part because another RAD51 paralog, RAD51C, had previously been identified as a FA gene (Vaz et al., 2010). However, as loss-of-function mutations were present in other genes, XRCC2 could not be reliably established as causative for the clinical phenotype in this initial study. A subsequent study demonstrated that XRCC2 (FANCU) is indeed the 20th FA gene based on the correction, following expression of XRCC2, of cellular phenotypes that are characteristic of FA cells (Park et al., 2016). These phenotypes included complementation of cellular hypersensitivity to MMC, correction of MMC-induced chromosome aberrations (total aberrations including breaks, gaps, radial and ring chromosomes, and number of radial chromosomes specifically), and MMC-induced cell cycle accumulation in G2-M (Park et al., 2016). However, the patient had normal blood counts and had not displayed cancer through age 7 (Park et al., 2016; Shamseldin et al., 2012).

To date, 22 FA or FA-like genes have been identified (Nepal et al., 2017). FA genes are autosomal recessive tumor suppressor genes, except for the X-linked FANCB and the autosomal dominant RAD51 (FANCR). The monoubiquitination of the FANCD2/ FANCI protein dimer is the central step in the FA pathway. FANC -A, -B, -C -E, -F, CC: TXT: -G ID: 295>, -L, -M, UBE2T (FANC-T) are early (or upstream) FA genes, since loss of function mutations in any of these genes results in defective monoubiquitination of FANCD2/I (Mamrak et al., 2017; Nepal et al., 2017). Late/downstream FA genes, which are associated with normal monoubiquitination of FANCD2 and FANCI when mutated include: BRCA2 (FANCD1), BRIP1 (FANCJ), PALB2 (FANCN), RAD51C (FANCO), RAD51 (FANCR), BRCA1 (FANCS), XRCC2 (FANCU), MAD2L2 (FANCV/polTheta) and RFWD3 (FANCW). Typical of late/downstream FA genes, FA-U cells display defective assembly of RAD51 foci in response to DNA damage (Park et al., 2016).

The vast majority of FA patients have bi-allelic mutations in the upstream FA genes, notably FANCA, FANCC and FANCG, and display clinical features characteristic of FA. These include progressive bone marrow failure around 7.6 years of age, a variety of congenital anomalies, and a predisposition to acute myeloid leukemia as well as various solid tumors that occur in the second and third decade of life (Kutler et al., 2003). Microcephaly, short stature, skin pigmentation defects, hypogonadism, and radial ray anomalies, many of which were observed in the single FA-U patient identified until present, are among the congenital anomalies that are often observed. Endocrine abnormalities are also seen in a significant number of FA patients (Rose et al., 2012).

Certain other FA complementation groups such as FA-O, defined by RAD51C (FANCO) mutations, and FA-R, defined by heterozygous dominant-negative RAD51 (FANCR) mutation, have been designated atypical FA (or FA-like) because of the absence of bone marrow failure and no increased incidences of cancer (Park et al., 2016). However, bone marrow failure and cancer are not always observed for every patient in each FA complementation group and the single FA-U patient identified so far has not reached the age at which these features are frequently observed (Kutler et al., 2003). Therefore it is not yet clear whether or not patients with germ-line bi-allelic defects in XRCC2 represent atypical FA.

Breast Cancer

Disease

In a collaborative exome-sequencing study involving patients from the Netherlands, Spain and Australia, Park et al. identified 6 out of 1308 patients with early-onset breast cancer as having likely deleterious mutations in XRCC2, while none of the 1,120 controls carried such a mutation. Two of the six mutations were frameshift mutations (p.Arg17* and p.Cys217*) and 4 of the 6 were missense alterations with single a.a. exchanges that were predicted by three algorithms to be associated with a loss-of-function (Park et al., 2012). As the frequency at which these variants occurred in breast cancer patients, as compared to controls, was statistically significant, XRCC2 was identified by the authors as a low frequency breast cancer susceptibility gene.

However, no other study so far has confirmed mutation of XRCC2 as a significant cause of inherited breast cancer (Hilbers et al., 2016; Hilbers et al., 2012; Pelttari et al., 2015). For example, Hilbers et al. analysed the coding region of 3548 non-BRCA1/2 familial breast cancer cases and 1435 healthy controls (Hilbers et al., 2012). In the patient group, they detected only one patient with a protein truncation mutation and 20 patients with missense alterations, as compared to nine controls with missense variants. Importantly, in 2016, Hilbers et al. functionally analyzed all nonsynonymous coding variants from the two major studies published in 2012 (Hilbers et al., 2012; Park et al., 2012). Out of 24 missense alterations, only four variants had a reduced functional activity with 50-75% rescue in two out of three assays (Hilbers et al., 2016).

Finally, Decker et al. sequenced the XRCC2 coding region of 13,087 breast cancer patients and 5488 healthy controls from the UK (Decker et al., 2017). Only 13 carriers of truncating XRCC2 variants were found, nine in breast cancer patients and four in controls. There were also no statistical differences for 32 rare missense variants between the patient and control groups. Thus these authors concluded that truncating/loss-of-function mutations in XRCC2 are not associated with an increased risk of breast cancer (Decker et al., 2017), and therefore germ-line mutation of XRCC2 is not a major cause of inherited breast cancer (Decker et al., 2017; Hilbers et al., 2012).

Prognosis

Because XRCC2 has an important role in HR, it is likely that tumors with loss-of-function of XRCC2 may be particularly responsive to poly (ADP-ribose) polymerase (PARP) inhibitors. In support of this possibility, FA cells from the FANCU complementation group, which have biallelic mutation of XRCC2, have increased sensitivity to the PARP inhibitor olaparib, as compared to complemented cells (Park et al., 2016). Thus, identification of breast cancer patients, and perhaps other cancer patients, with deleterious somatic variants of XRCC2 may be a basis for such personalized treatments.

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