Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

FANCL (FA complementation group L)

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Published in Atlas Database: June 2019
Online updated version : http://AtlasGeneticsOncology.org/Genes/FANCLID40529ch2p16.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70722/06-2019-FANCLID40529ch2p16.pdf
DOI: 10.4267/2042/70722

Abstract

FANCL is the catalytically active component of the Fanconi anemia (FA) DNA repair pathway that maintains genomic stability by recognizing and repairing interstand cross links (ICL), and DNA damage incurred during replication.
The FA pathway is comprised of 22 genes, biallelic mutations in any one of these genes causes Fanconi anemia, a cancer pre-disposition syndrome characterized by chromosomal instability and hypersensitivity to DNA crosslinking agents, such as those used in chemotherapy like mitomycin C (MMC) (Niraj, Färkkilä et al., 2019).
FANCL acts within the 9 protein FA "core complex" (FANCA, FANCG, FAAP20 (AG20), FANCC, FANCE, FANCF (CEF), FANCB, FANCL, FAAP100 (BL100) that forms in response to DNA damage. Together with E2 conjugating enzyme Ube2t (FANCT), the E3 RING ligase FANCL monoubiquitinates FANCD2 and FANCI (ID2), this signals downstream repair processes, and is defective in 95% of all FA patients (Inc, 2014).

Keywords
FANCL, RING E3 ligase, Fanconi Anemia, ubiquitination, cancer pre-disposition

Identity

Other names: PHF9, FAAP43, POG

HGNC (Hugo): FANCL

Location
FANCL is located on 2p16.1 which is the short arm (p) of chromosome 2 at position 16.1 between base pairs 58,159,243 to 58,241,681.

DNA/RNA

FANCL has 2 described isoforms produced by alternative splicing. Isoform one (Q9NW38-1). Is known as the canonical isoform, while isoform 2 (Q9NW38-2) differs from the canonical sequence at 178-178: T--> TPQVNS.

Figure 1: Genomic context of FANCL on chromosome 2 (Adapted from NCBI).

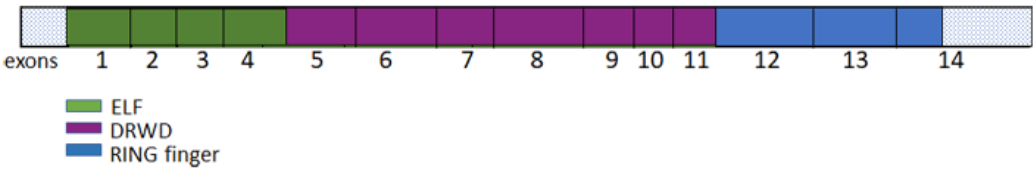

Figure 2: Exons in FANCL gene. Colour coded to indicate ELF, DRWD, and RING finger domains. Adapted from Chandrasekharappa et al. 2013.

Protein

Description

The FANCL gene encodes FANCL protein comprised of 375 amino acids with a molecular mass of 42905 Da. FANCL is comprised of 3 domains, an N-terminal E2-like fold (ELF), a novel double-RWD (DRWD) and C-terminal RING domain (Hodson, Purkiss et al., 2014).

Expression

From total RNA sequencing, FANCL was found to be expressed in adrenal gland (RPKM 2.1), prostate (RPKM 2.34), thymus (RPKM 2.1), and thyroid (RPKM 2.2) (Bioproject PRJNA280600 (PMID 25970244).

In another RNA sequencing project on 27 different tissues from 95 human individuals, FANCL was highly expressed in adrenal gland (RPKM 16.8), endometrium (RPKM 10.6), lymph nodes (RPKM 8.5), ovary (RPKM 9.2), prostate (RPKM 8.5), and testis (RPKM 12) (Bioproject PRJEB4337, PMID 24309898).

Function

FANCL the catalytically active part of the 9 protein Fanconi anemia (FA) core complex comprised of FANCB, FAAP100, FANCA, FANCG, FAAP20, FANCC, FANCE and FANCF that forms in response to DNA damage incurred during DNA replication in S-phase, or to detection of interstand cross links (ICL) (Ceccaldi, Sarangi et al., 2016). FANCL is an E3 ubiquitin ligase that specifically monoubiquitinates FANCD2 (at lysine 561) and FANCI (at lysine 523) (ID2; Note the FANCD2-FANCI heterodimer "ID2" must not to be confused with the gene ID2) in the presence ofUBE2T (FANCT) to signal downstream DNA repair proteins.

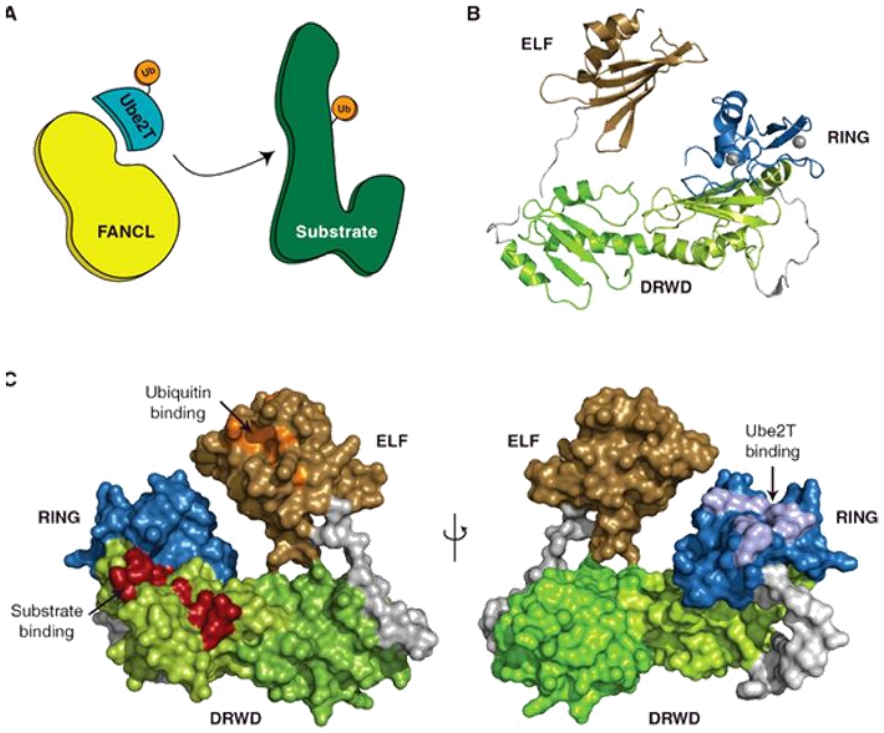

Figure 3: A) Schematic of D2 monoubiquitination by E3 RING ligase FANCL and E2 conjugating enzyme. B) Ribbon diagram of FANCL with ELF domain (brown), DRWD domain (green), and RING domain (green). C) Surface representation of protein binding domains on FANCL. The binding patch for ubiquitin (orange) is within the ELF domain, while the substrate binding domain (red) is in the DRWD domain, and the Ube2t binding domain (light purple) is in the RING domain. Figure from Specificity and disease in the ubiquitin system by Viduth K. Chaugule and Helen Walden in Biochemical Society Transactions Feb 2016, 44 (1) 212-227; DOI: 10.1042/BST20150209.

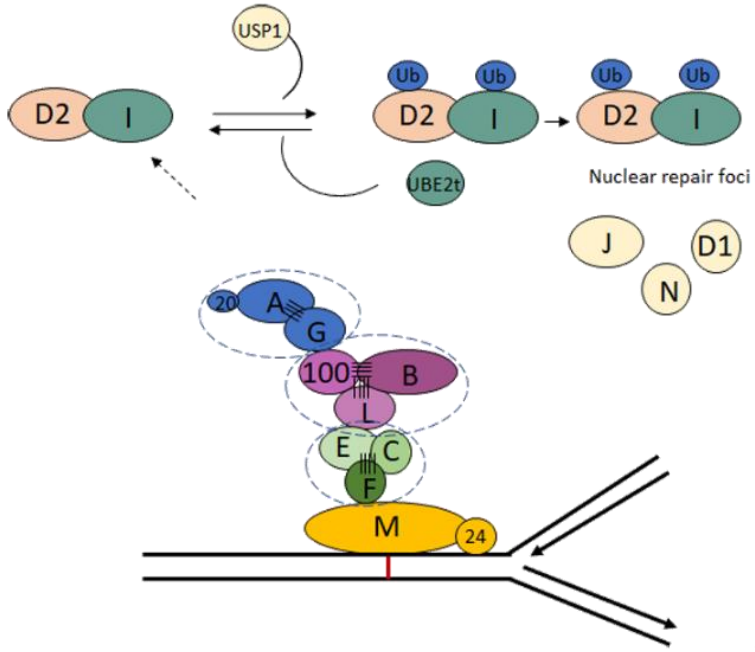

Figure 4: Schematic of Fanconi Anemia DNA damage response pathway. In response to interstrand cross links (ICL), or DNA damage from DNA replication, FANCM recruits the 9 protein core complex to DNA damage sites to monoubiquitinate FANC D2 and I. The core complex is comprised of 3 sub-complexes AG20 (FANC A, G, FAAP20), BL100 (FANC B, L, FAAP100), and CEF (FANC C,E,F). Dashed lines indicate groupings of sub-complexes, while triple lines indicate putative direct protein interactions. Within the core complex, FANCL has a RING E3 domain with ubiquitin ligase activity, but mutation in any one of the FA genes leads to defective DNA repair. Ubiquitinated ID2 is activated, and localized to chromatin in nuclear foci to interact with downstream DNA repair proteins (FANCD1, FANCD1, FANCN) to repair DNA via homologous recombination. Once DNA repair is completed, USP1 deubiquitinates ID2 so that DNA damage response can be reinitiated. Figure adapted from https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/fancb

FANCL is comprised of 3 distinct functional domains: the RING domain interacts with the E2 conjugating enzyme UBE2T (FANCT), the central DRWD domain interacts with FANCD2, and the N-terminal E2-like fold domain (ELF) domain interacts with ubiquitin (Hodson et al., 2014, Miles, Frost et al., 2015).

Within the core complex, FANCL interacts as a subcomplex with FANCB and FAAP100 (Huang, Leung et al., 2014, van Twest, Murphy et al., 2017); both proteins stabilize FANCL (Rajendra, Oestergaard et al., 2014), and enhance it's activity 5-fold in vitro assays (Ling, Ishiai et al., 2007).

Along with FANCA, FANCG, FANCF, FANCL was found to interact directly with hairy enhancer of split 1 (HES1), which is a part of the NOTCH1 developmental pathway involved hematopoietic stem cell (HSC) self-renewal (Tremblay, Huang et al., 2008).

Depletion of HES1 from cells resulted in FA-like phenotype with disrupted interaction between individual core complex proteins, increased cell sensitivity to DNA crosslinking agents, and reduced MMC-induced ID2 monoubiquitination (Tremblay et al., 2008).

Finally HES1 did not interact FA-mutated core complex proteins. HSC defects and eventual bone marrow failure in FA patients may be linked to inability of HES1 to interact with a defective core complex (Tremblay et al., 2008, Tremblay, Huang et al., 2018).

Mutations

Germinal

FANCL-associated Fanconi anemia is inherited in an autosomal recessive manner, and accounts for 0.2% of all FA cases (Wu, Liu et al., 2017). To date, there are only 9 documented cases of FANCL-associated FA (Ali, Kirby et al., 2009, Ameziane, Sie et al., 2012, Chandrasekharappa, Lach et al., 2013, Meetei, de Winter et al., 2003, Vetro, Iascone et al., 2015, Wu et al., 2017).

Of the 5 cases with phenotypic and genotypic data, four were severe, and one was mild. Two severe cases frame shift deletions in exon 4 and 6 that truncated FANC, resulted in postnatal mortality and presented with VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal malformations, and limb defects) (Vetro et al., 2015). Another case with homozygous frameshift insertion of exon 9 had a severe phenotype with esophageal atresia (Ameziane et al., 2012). Finally, a novel homozygous mutation c.822_823insCTTTCAGG (p.Asp275LeufsX13) had a typical FA presentation with progression to bone marrow failture and death at age 9 from acute myelomonocytic leukemia (AML-M4) (Wu et al.,

2017). The patient with mild FANCL-associated FA had bi-allelic mutation (Ali et al., 2009). One allele had an in-frame 3-bp deletion c.1007_1009delTAT (p.Ile336_Cys337delinsSer) in exon 12 within the PHD/RING-finger domain that resulted in loss of one amino acid, isoleucine-336, and conversion of cysteine-337 to serine null mutation (produces non-function protein). The other mutated allele had a 4-bp duplication (c.1095_1098dupAATT (p.Thr367AsnfsX13) that resulted in a frameshift just outside the RING-finger domain in exon 14. 4-bp duplication mutation is a hypomorphic mutation (produces partially functional protein) (Ali et al., 2009).

Sequencing screen of 27 FA cases with unidentified mutations uncovered 3 FANCL FA associated mutations: c.375-2033C>G (skips exons 4,6,7), c.375-2033 C>G (multiple splicing aberrations), c.1092G>A (skips exon 13), but didn't have corresponding phenotypic data

(Chandrasekharappa et al., 2013). There is no phenotypic data for the first FANCL-associated FA patient that had exon 11 deletion and insertion of 177-nt sequence (Meetei et al., 2003).

Implicated in

Fanconi Anemia

Disease

Biallelic mutations in FANCL, or any of the other 21 FA pathway proteins is implicated in Fanconi Anemia (FA), a rare genetic condition that results in progressive bone marrow failure (pancytopenia), congenital malformations in 75% of patients (short stature, urogenital defects, café au lait spots, skeletal malformations), and cancer pre-disposition (primarily acute myeloid leukaemia, and certain solid tumours) (Alter, 2014).

Mutations that result in loss-of-function of both FANCL alleles may correlate with more severe phenotypes (Vetro et al., 2015). Hydrocephalus-VACTERL (vertebral, anal, cardiac, tracheo-esophageal fistula, renal, and limb anomalies) syndrome has been reported in two FANCL-linked FA patients that died shortly after birth (Vetro et al., 2015).

Prognosis: The prognosis for FA is poor as there is no cure, and the average lifespan is 20-30 years. If no congenital abnormalities are apparent at birth, patients are often diagnosed with FA when they present with aplastic anemia ages 8-10 (>700 fold risk) (Alter, 2014). Bone marrow transplants are often conducted to correct the haematological issues associated with FA, however due to faulty DNA repair FA patients retain high cancer risk particularly leukaemia, and head and neck squamous cell carcinomas (approximately 500 fold risk) (Shimamura Alter, 2010).

Diagnosis: Diagnostics for FA is done with a chromosomal breakage test; when treated with interstand crosslinking agents such as mitomycin C (MMC) or diepoxybutane (DEB) FA cells exhibit high number chromosomal breakages, and abnormalities as compared to normal cells.

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This article should be referenced as such:

van Twest S, Deans A. FANCL (FA complementation group L). Atlas Genet Cytogenet Oncol Haematol. 2020; 24(5):189-193.