FANCB (FA complementation group B)

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Abstract

FANCB protein is a component of the Fanconi Anemia (FA) core complex needed for DNA repair. Within the core complex, FANCB forms a protein subcomplex with two other proteins, FAAP100, and an E3 RING ligase FANCL (BL100) to monoubiquitinate FANCD2 and FANCI (ID2), a process that is defective in 95% of all FA patients. FA is a rare, genetic cancer pre-disposition syndrome characterized by chromosomal instability and hypersensitivity to DNA crosslinking agents, such as those used in chemotherapy like mitomycin C (MMC) (Kennedy D’Andrea, 2006). FANCB is the only known X-linked FA gene, and mutations account for 1% of FA cases (Alter Rosenberg, 2013).

Keywords: FANCB, Fanconi Anemia; Ubiquitination, VACTERL-H; Cancer pre-disposition; Chromosome X

Identity

Other names: FAB, FA2, FACB

HGNC (Hugo): FANCB
Location: Xp22.2

DNA/RNA

Description

FANCB has 10 exons, and the translation start site is in exon 3 (Meetei et al., 2004).

Transcription

The FANCB gene undergoes X-inactivation. The mutated FANCB allele is preferentially inactivated in female carriers (so the wild-type allele is expressed), while males with mutations in FANCB get FA (Meetei et al., 2004). FANCB linked FA accounts for 1% of FA cases, and only affects male patients.

Figure 1: Genomic context of FANCB on chromosome (Adapted from NCBI).
FANCB (FA complementation group B)

van Twest S, Deans A

Atlas Genet Cytogenet Oncol Haematol. 2020; 24(1)

19

Protein

Description
The FANCB gene encodes FANCB protein comprised of 859 amino acids, with a molecular mass of 97726 Da. It has a putative C-terminal nuclear localization signal (Meetei et al., 2004).

Expression
Low expression in tissues. Results from Illumina bodyMap2 transcriptome (BioProject: PRJEB2445) of high throughput sequencing of individual and mixture of 16 human tissue RNA showed highest expression in white blood cells (mean RPKM 0.32), testes (mean RPKM 0.23), brain (mean RPKM 0.168), adrenal (mean RPKM 0.164), ovary (mean RPKM 0.153), and lymph nodes (mean PRKM 0.149). Another RNA sequencing project of total RNA from 20 human tissues (BioProject: PRJNA280600) found highest FANCB expression in brain cerebellum (mean RPKM 0.789), and thymus (mean RPKM 0.524). BioProject PRJEB4337 performed HPA RNA sequencing of normal tissues found highest FANCB expression in bone marrow and in lymph nodes.

BioProject PRJNA270632 looked at tissue specific FANCB RNA induction during human fetal development from 6 tissues between 10-20 weeks gestational time.

Function
FANCB is a component of the Fanconi Anemia 9 protein "core complex" that acts as a multiunit ubiquitin ligase to ubiquitinate FANCD2 and FANCI in response to DNA damage incurred during DNA replication in S-phase, or to detection of interstand cross links (ICL) (Ceccaldi, Sarangi, D'Andrea, 2016). The key event in the FA pathway is the monoubiquitination of ID2 that activates downstream DNA repair proteins. The core complex is comprised of 3 separate sub-complexes, FANCG, FAAP20 (AG20), FANCC, FANC E, FANCF (CEF), and FANCB, FANCL, FAAP100 (BL100) (Huang et al., 2014; Medhurst et al., 2006). The BL100 sub-complex is critical to core complex assembly as it forms a bridge between AG20 and CEF (van Twest et al., 2017). The BL100 subcomplex is dimeric, and FANCB homodimer forms the interface between two copies of FANCL (a RING E3 ligase), and FAAP100 to simultaneously ubiquitinate FANCD2 and FANCI (ID2) (Swuec et al., 2016; van Twest et al., 2017). Correspondingly, FANCB and FAAP100 stabilize FANCL (Rajendra et al., 2014), and enhance its activity by 5-fold in invitro assays (Ling et al., 2007). Mutation in any one of the 19 FA genes results in defective DNA repair.

Mutations
Somatic
Somatic FANCB mutations are very rare, and may occur at normal mutagenesis rate. Small insertions, point mutations, and large deletions have been reported in the FANCB gene (MccAuley et al., 2011; Meetei et al., 2004). Most FANCB mutations result in truncation of the encoded protein.
FANCB (FA complementation group B)

van Twest S, Deans A

Atlas Genet Cytogenet Oncol Haematol. 2020; 24(1)

**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, PALB2 (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.

**Implicated in**

**Fanconi Anemia**

**Disease**

Mutated FANCB 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).

As the only X-linked FA gene, FANCB accounts for 1% of FA cases, in all other instances FA is autosomal recessive. Mutations in FANCB (and all other core complex FA proteins) is associated with hypersensitivity to DNA-damaging agents, chromosomal instability with increased chromosome breakage and defective DNA repair. In addition to FA, some patients with FANCB mutations also exhibit hydrocephalus-VACTERL (vertebral, anal, cardiac, tracheo-esophageal fistula, renal, and limb anomalies) syndrome. A frameshift FANCB mutation that results in a truncated protein (stop codon at position 446) was associated with
VACTERL-H (Holden et al., 2006; McCauley et al., 2011).

**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).

**Diagnostic**

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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