Title: Fanconi Anemia *GeneReview* – Molecular Genetics of Less Commonly Involved Genes

Authors: Mehta PA, Tolar J

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Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

ERCC4

Gene structure. *ERCC4* has 11 exons (NM_005236.2)

Pathogenic allelic variants. See Table A.

Normal gene product. ERCC4 (NP_005227.1; 916 amino acids) is an excision and cross-link repair protein that plays a role ion DNA stability and repair of DNA damage. Aside from Fanconi anemia, aberrant *ERCC4* has been associated with Conskayne syndrome, xeroderma pigmentosum, and breast/ovarian cancer [Bogliolo et al 2013, Kashiyama et al 2013].

Abnormal gene product. See Molecular Genetic Pathogenesis.

FANCL

Gene structure. *FANCL* has 14 exons (NM_018062.2).

Pathogenic allelic variants. See Table A.

Normal gene product. The E3 ubiquitin-protein ligase FANCL has 375 amino acids. It is a component of the FA core complex with three WD40 (Tryptophan-Aspartate -40) repeats and a PHD finger motif (a variant RING finger motif) [Meetei et al 2003] and is presumed to be the catalytic subunit of the FA core complex as an ubiquitin ligase for FANCD2 and FANCI [Hodson et al 2011, Miles et al 2015]. FANCL directly interact with UBE2T (E2 ubiquitin conjugating enzyme) [Machida et al 2006, Hodson et al 2014]. A baculoviral generated protein has been shown to have in vitro monoubiquitylation activity [Alpi et al 2008]. FANCL is relevant to normal development as is evidenced by its dysfunction linked to VACTERL association [Vetro et al 2015].

Abnormal gene product. See Molecular Genetic Pathogenesis.

FANCM

Gene structure. *FANCM* has 23 exons (NM_020937.1).

Pathogenic allelic variants. See Table A.

Normal gene product. The Fanconi anemia group M protein (FANCM) has 2048 animo acids. It is a component of the FA core complex, contains the seven helicase-specific motifs, one degenerate endonuclease domain, and ssDNA and dsDNA-stimulated ATPase activity and DNA translocase activity [Meetei et al 2005, Singh et al 2013]. FANCM is phosphorylated in response to DNA damage and complexes with the

histone-fold complex MHF [Tao et al 2012, Fox et al 2014, Girard et al 2014, Xue et al 2015]. In concert with FAAP24, a FANCM binding protein [Coulthard et al 2013], FANCM participates in a checkpoint reaction to DNA damage, nucleotide excision repair, and maintenance of genome stability [Deans & West 2009, Huang et al 2010, Kelsall et al 2012, Wang et al 2013].

Abnormal gene product. See Molecular Genetic Pathogenesis.

PALB2 (previously FANCN)

Gene structure. *PALB2* has 13 exons (NM_024675.3).

Pathogenic allelic variants. See Table A.

Normal gene product. PALB2, the partner and localizer of BRCA2 protein, has 1186 amino acids. It regulates localization and stability of BRCA2 protein. Short sections of the PALB2 N-terminus share homologies with a segment of prefoldin and the light chain 3 (LC3) of microtubule-associated protein MAP1. PALB2 also has two WD40 repeat-like segments at the C terminus [Xia et al 2006]. *PALB2* is one of the FA-related genes that is also a breast cancer susceptibility gene. It is a known protein partner of FANCD1/BRCA2 and plays a role in the homologous recombination repair pathway [Xia et al 2007, Guo et al 2015].

Abnormal gene product. See Molecular Genetic Pathogenesis.

RAD51C

Gene structure. *RAD51C* has nine exons (NM_058216).

Pathogenic allelic variants. See Table A.

Normal gene product. RAD51C is a protein of 376 amino acids shown to participate in several distinct protein complexes involved in homologous recombination [Somyajit et al 2012]. RAD51 variants have been demonstrated to bind to single strand overhangs that occur after processing of DNA lesions in concert with BRCA2 [Somyajit et al 2010].

Abnormal gene product. See Molecular Genetic Pathogenesis.

SLX4

Gene structure. *SLX4* has 15 exons (reference sequence NM_032444).

Pathogenic allelic variants. See Table A.

Normal gene product. SLX4 is a protein of 1834 amino acids involved in resolution of homologous recombination intermediates, such as Holliday junctions [Kim et al 2011, Stoepker et al 2011]. SLX4 interacts with other endonuclease complexes, including MUS81-EME1 and XPF-ERCC1 [Kim et al 2011, Stoepker et al 2011], interacts with XPF (ERCC4, FANCQ) [Bogliolo et al 2013, Kashiyama et al 2013, Hashimoto et al 2015], and is operational in multiple aspects of genome maintenance [Cybulski & Howlett 2011, Kim et al 2011, Salewsky et al 2012, Schuster et al 2013, Kim 2014].

Abnormal gene product. See Molecular Genetic Pathogenesis.

UBE2T

Gene structure. *UBE2T* has six exons (NM_001310326).

Pathogenic allelic variants. See Table A.

Normal gene product. UBE2T is a protein of 197 amino acids. It functions as E2 conjugase that interacts with FANCL and mediates monoubiquination of FANCD2 and FANCI. Critically, it is not a member of the FA core complex of proteins, but rather is recruited to damaged chromatin independently [Machida et al 2006, Alpi et al 2007, Longerich et al 2014, Hira et al 2015, Miles et al 2015, Rickman et al 2015, Virts et al 2015].

Abnormal gene product. See Molecular Genetic Pathogenesis.

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