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Fanconi anemia: a model disease for studies on human genetics and advanced therapeutics

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Fanconi anemia (FA) is characterized by bone marrow failure, malformations, and chromosome fragility. We review the recent discovery of FA genes and efforts to develop genetic therapies for FA in the last five years. Because current data exclude FANCM as an FA gene, 15 genes remain bona fide FA genes and three (*FANCO*, *FANCR* and *FANCS*) cause an FA like syndrome. Monoallelic mutations in 6 FA associated genes (*FANCD1*, *FANCJ*, *FANCM*, *FANCN*, *FANCO* and *FANCS*) predispose to breast and ovarian cancer. The products of all these genes are involved in the repair of stalled DNA replication forks by unhooking DNA interstrand cross-links and promoting homologous recombination. The genetic characterization of patients with FA is essential for developing therapies, including hematopoietic stem cell transplantation from a savior sibling donor after embryo selection, gene therapy, or genome editing using genetic recombination or engineered nucleases. Newly acquired knowledge about FA promises to provide therapeutic strategies in the near future.

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Introduction: Fanconi anemia and Fanconi anemia-like genes

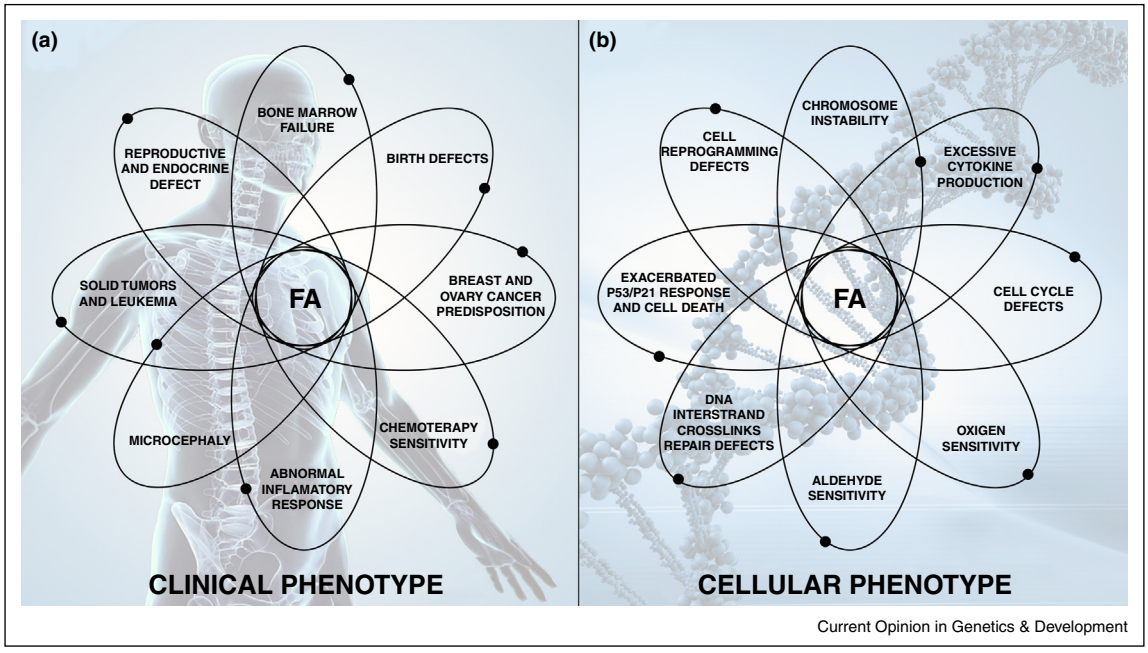
Fanconi anemia (FA), which affects approximately 1–3 of 500 000 newborns, causes bone marrow failure (BMF), malformations, and cancer predisposition. Hallmarks of FA are chromosome fragility and hypersensitivity to drugs that induce DNA interstrand cross-links (ICLs). Numerous other physiological and cellular abnormalities likely contribute to pathogenesis (Figure 1). The current decade has been prolific for the discovery of novel FA genes. Thus, 19 genes are associated with FA, including the recently discovered genes *FANCO/RAD51C* [1••], *FANCP/SLX4* [2••,3••], *FANCQ/ERCC4* [4••], *FANCR/RAD51* [5••], *FANCS/BRCA1* [6••] and *FANCT/UBE2T* [7••,8••,9••]. However, following a stringent criteria of at least two patients with BMF and a positive chromosome fragility test, only 15 are classified as bona fide FA genes (*FANCA*, *B*, *C*, *D1*, *D2*, *E*, *F*, *G*, *I*, *J*, *L*, *N*, *P*, *Q* and *T*). *FANCO*, *FANCR* and *FANCS* are FA-like genes, because they cause a chromosome fragility syndrome with FA-related malformations but without BMF (Figure 2). *FANCM* should also be excluded from the list of FA genes, because only one patient is reported to carry biallelic mutations [10]. It was subsequently found that this individual also carries biallelic *FANCA* mutations and has a sibling subtyped as FANCA. Notably, FANCM fails to complement the genetic defect of this patient [11]. Moreover, loss-of-function FANCM variants are more common than originally predicted and two individuals of Finnish descent with loss of function *FANCM* variants are healthy and exhibit normal hematology [12•]. Thus, we recommend excluding *FANCM* as an FA gene, although, together with FAAP100, FAAP25, and other FA-core complex interacting proteins, FANCM is involved in the FA ICL repair (ICLR) pathway (see below). Similarly, whole exome sequencing (WES) detected biallelic *XRCC2* mutations in a consanguineous FA family [13]; however, this is again a single case and, because of the lack of genetic complementation data or any other functional evidence of a causative role of this homozygous mutation in disease, *XRCC2* should not yet be considered an FA gene.

The genetic heterogeneity and the number of private and founder mutations make the mutational analysis of FA patients extremely difficult and time consuming by traditional techniques such as Sanger sequencing [14–16]. However, next-generation sequencing (NGS) technologies, including WES or targeted sequencing of FA genes, together with high-resolution methods to detect large deletions, such as comparative genome hybridization arrays, single-nucleotide polymorphism arrays, and targeted Multiplex Ligation-dependent Probe Amplification, are now being implemented to find the underlying FA gene and determine the pathogenic mutations of new patients with FA [4••,17–21].

FA genes that predispose to breast and ovarian cancer

FANCD1/BRCA2, *FANCS/BRCA1*, *FANCJ/BRIP1*, *FANCM*, *FANCN/PALB2*, and *FANCO/RAD51 C* are breast

Figure 1



FA clinical and cellular phenotypes. **(a)** A wide range of clinical features, all of them of incomplete penetrance, characterizes the FA clinical phenotype. The main FA clinical features can be organized in four fundamental categories: abnormal embryo development (birth defects, microcephaly), bone marrow failure, reproductive and endocrine defects and cancer predisposition including solid tumors and leukemia. In some genetic subtypes the disease is linked to breast and ovarian cancer predisposition in monoallelic carriers and some adult FA patients. **(b)** The hallmark of FA cells is a DNA repair defect that causes cellular sensitivity to ICL-inducing agents, chromosome instability and cell cycle alterations. FA cells have several other phenotypic abnormalities most probably related to the DNA repair defect such as the oxygen and aldehyde sensitivity, increased cell death and the cell reprogramming defects. Additionally, FA cells overproduce proinflamatory cytokines that are known to be proapoptotic for HSC. All these characteristics are probably related to each other and their combination together with stochastic factors account for the clinical phenotype of FA patients.

and ovarian cancer susceptibility genes in carriers of monoallelic mutations (Figure 1) highlighting the fundamental link between FA and familial breast and ovarian cancer (FBOC). *RAD51 C* mutations influence ovarian cancers more than breast cancers [22,23], and are linked to other tumors such as head and neck cancer [24,25]. *RAD51 C* and *FANCM* were initially associated to FA before they were candidates for FBOC in monoallelic carriers [26••,27•] highlighting the fundamental role of FA research in advancing molecular oncology.

Historically, only FA genes (see below; Figure 2) with a direct role in the homologous recombination repair (HRR) late step of the FA pathway are linked to FBOC [28,29]. The two recently identified FA genes *FANCP/SLX4* and *FANCQ/ERCC4* were also excluded as major breast cancer susceptibility genes in Italian, German, Spanish, Estonian, Jewish, and non-Jewish American populations [30–37]. However, pathogenic mutations in *FANCM* are associated with breast cancer susceptibility in several populations [27•,38], suggesting a core complex-independent role (see below) of FANCM. In fact, even though FANCM is not essential for RAD51 foci formation and HRR, the camptothecin sensitivity of FANCM cells is shared with FANCD1 and FANCN cells, linking FANCM to the step of the FA pathway connected to HRR [11].

The Fanconi anemia pathway: find, unhook, bypass, and recombine

ICLs are highly damaging, because they impede transcription and replication-fork progression. Since they affect both DNA strands, ICLs complicate error-free DNA repair, because an undamaged DNA template is not available. The FA DNA repair pathway coordinates reactions that remove ICL damage to restore genome integrity (for more detailed reviews, see [39,40]). Eight FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM) form a nuclear complex (FANCore) whose ubiquitin E3 ligase function is activated by blocked DNA replication forks (Figure 3). The activated FANCore complex monoubiquitinates the FANCD2–FANCI heterodimer (ID complex) and UBE2T/FANCT provides the E2 conjugase activity necessary to this process [41–43]. The activated ID complex relocates to the damaged DNA in an ATR and BRCA1-dependent manner [41,43,44], promotes nucleolytic cleavage of the 3′ and 5′ sites of DNA to