Nebert et al. Human Genomics (2016) 10:25
DOI 10.1186/s40246-016-0081-3

Human Genomics

LETTER TO THE EDITOR Open Access

Letter to the editor for "Update of the human and mouse Fanconi anemia genes"

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After our review of the "Update of the human and mouse Fanconi anemia genes" had been published [1], a report appeared [2] that we believe contains additional important and clarifying information relevant to our discussion of the "Fanconi anemia pathway" and cross-talk with other DNA-repair pathways.

In Fig. 1, which is a modified version of the Figure 2 cartoon in our recent review [1], we had shown that, in response to upstream DNA damage signaling (such as phosphorylation by ATR/ATM) in the "FA/BRCA pathway," the FA core complex comprises at least 11 proteins. These include FANCA (A), FANCB (B), FANCC (C), FANCE (E), FANCF (F), FANCG (G), FANCM (M), and FANCL (L) proteins, plus three FAAP proteins (FAAP20, FAAP24, and FAAP100). This core complex binds UBE2T (T) by way of FANCL**;** the resultant complex then activates FANCD2/I dimers by means of mono-ubiquitination, and we had written that this is an essential prerequisite for repairing DNA interstrand cross-links.

The activated FANCD2/I (D2/I) complex then translocates to DNA damage sites and recruits downstream FA effector proteins. These include BRCA1 (S), BRCA2 (D1), RAD51 (R), BRIP1 (J), PALB2 (N), RAD51C (O), SLX4 (P), and ERCC4 (Q), plus other DNA-repair molecules (including FA-associated nuclease-1 (*FAN1*)), as illustrated as the orange ellipse at the far right in our Fig. 1 diagram [1]. This large complex then migrates to the site of the lesion to repair the DNA damage.

It had been presumed that FAN1, also required for interstrand cross-link repair, is recruited by ubiquitinated FANCD2/I (light green ellipse in Fig. 1) [1]. However, Lachaud and coworkers, using FAN1 nuclease-deficient mice, recently demonstrated [2] that recruitment of FAN1 by ubiquitinated FANCD2/I is not essential for interstrand cross-link repair. As an alternative, FAN1 recruitment and activity restrain DNA replication fork progression. This restraint, in turn, holds in check any chromosomal abnormalities from occurring, when the DNA replication forks stall. And this pause can happen––even in the absence of interstrand cross-links.

Consequently, recruitment of FAN1 by ubiquitinated FANCD2 may be regarded as facilitating the processing of stalled forks during DNA replication. Although this checkpoint process is essential for genome stability and improved overall well-being of the cell, it might better be described as not absolutely necessary. Therefore, a slightly revised *figure* is proposed here, in which FAN1 can be either bound or not bound from the remainder of this complex (comprising D2/I, S, D1, R, J, N, O, P, Q, and other DNA repair molecules). This *revised diagram* now takes into account the latest data published by Lachaud et al. [2].

Future experiments using other knockout mice will clarify this pathway further. Given the recent advances with CRISPR/*Cas9* methodology, knockout mouse lines––or cells in culture––can be efficiently created for all components shown in the *figure* herein, and then all permutations can be examined, one-by-one.

Acknowledgements
This work was supported in part by the NIH Grants AA022057 and AA021724 (VV), U41HG003345 (EAB), P30 ES006096 (DWN), and the Wellcome Trust grant 099129/Z/12/Z (EAB).

Authors' contributions
DWN drafted the manuscript. EAB, DCT, HJ, and VV edited the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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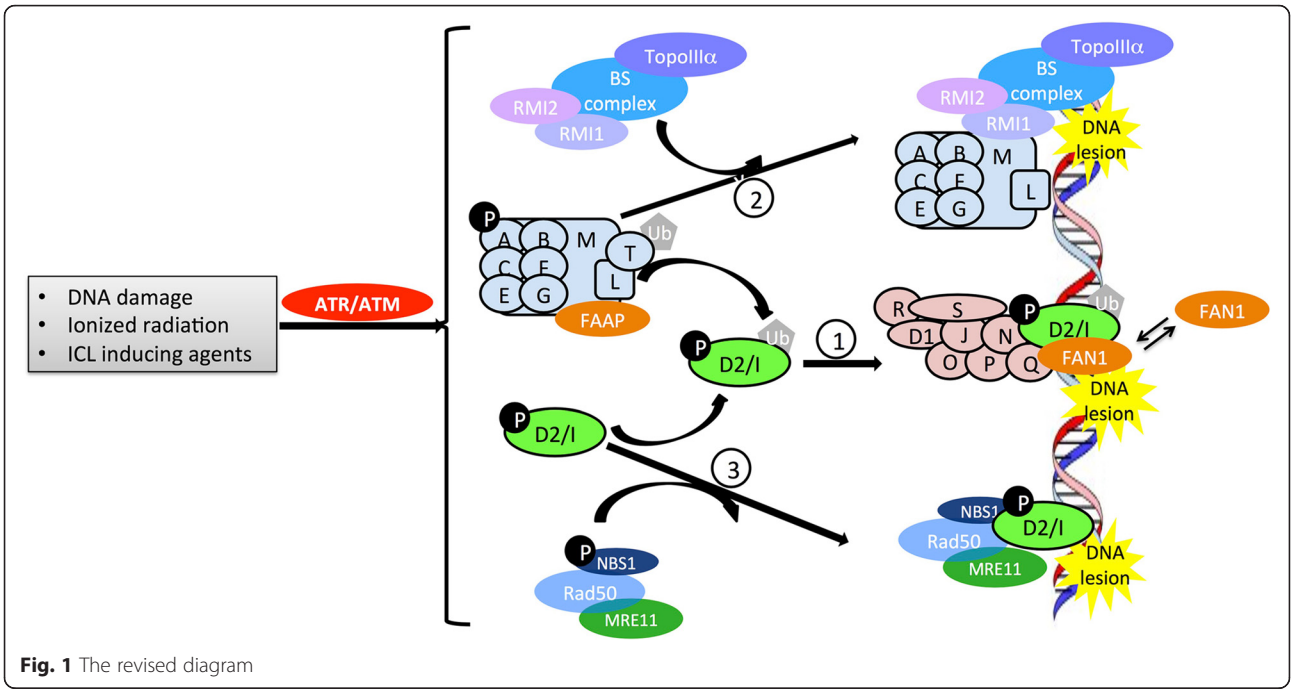

Fig. 1 The revised diagram

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Received: 14 May 2016 Accepted: 14 June 2016
Published online: 04 July 2016

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