Case Report: Sub-Clinical Fanconi Anemia in Siblings with Biallelic *BRIP1* Mutations

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BACKGROUND

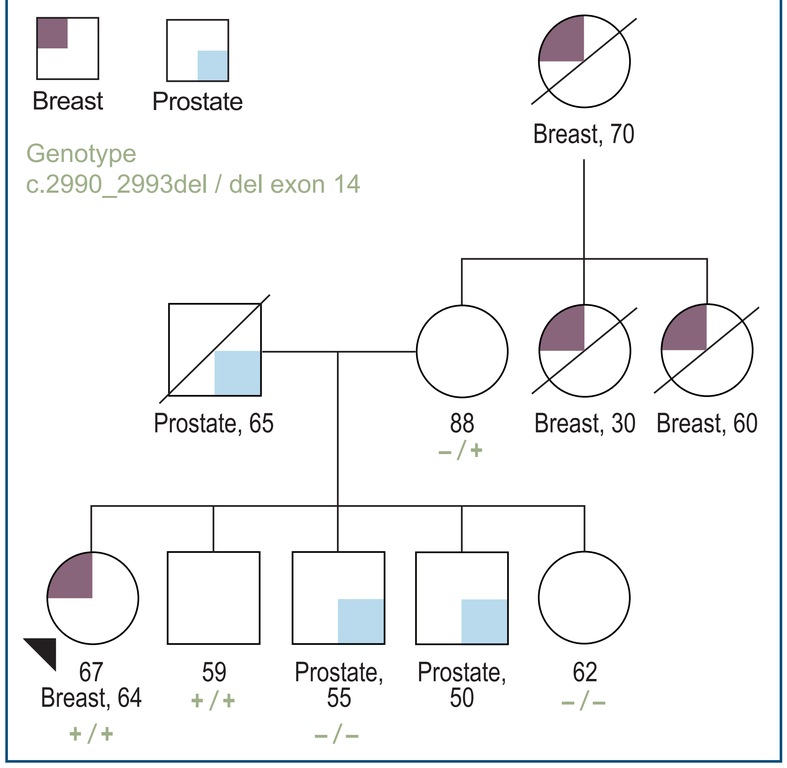
- Biallelic pathogenic variants (PVs) in some cancer-risk genes, such as *BRCA2*, cause Fanconi Anemia and have been studied extensively.
- However, there are only a few case reports describing the role of biallelic *BRIP1* mutations in Fanconi Anemia Complementation Group J (FANCJ).
- All reported cases presented with early onset bone marrow failure, short stature, and congenital abnormalities, which is consistent with a severe Fanconi Anemia phenotype.
- This case study describes siblings identified during hereditary cancer testing with a less severe presentation of Fanconi Anemia due to biallelic *BRIP1* PVs.

METHODS

- The proband had genetic testing with a 25-gene panel due to a personal and family history of breast cancer and was found to carry two different *BRIP1* PVs.
- Follow-up testing was performed to confirm that the PVs were on opposite alleles (RNA analysis on an additional sample from the proband, genetic testing of family members) and to establish a molecular diagnosis for Fanconi Anemia (chromosome breakage analysis (CBA) at Oregon Health Sciences University).
- Clinical information for the proband and tested family members was collected from provider-completed test request forms, and verified by verbal report from the individuals and their health care providers.

RESULTS

Figure 1. Pedigree of Case Report Family



- The 67 year-old female proband was found to carry biallelic *BRIP1* PVs.
  - c.2990_2993del and del exon 14
- Genetic testing was performed for the proband's mother and three siblings (Figure 1).
  - The mother carried only *BRIP1* del exon 14
  - Two siblings did not carry either PV
  - One brother carried both *BRIP1* PVs
- A molecular diagnosis of Fanconi Anemia was confirmed with CBA in the proband and her brother.
  - The clinical presentation of the proband and her brother were not typical of previously reported FANCJ cases (Table 1).
- We hypothesized that the atypical presentation may be explained if the *BRIP1* del exon 14 is only partially penetrant due to an alternate splice site; however, RNA analysis revealed that this is not the case (Figure 2).

Figure 2. PCR Products of the BRIP1 Transcript

Amplified mRNA products of the proband, age/gender matched blood controls, and normal breast and ovary tissues.

The proband shows two bands: one that aligns with the wild type mRNA product observed in controls (green box) and one that corresponds to a product with a deletion of exon 14 (red box).

There are no alternate mRNA transcripts present.

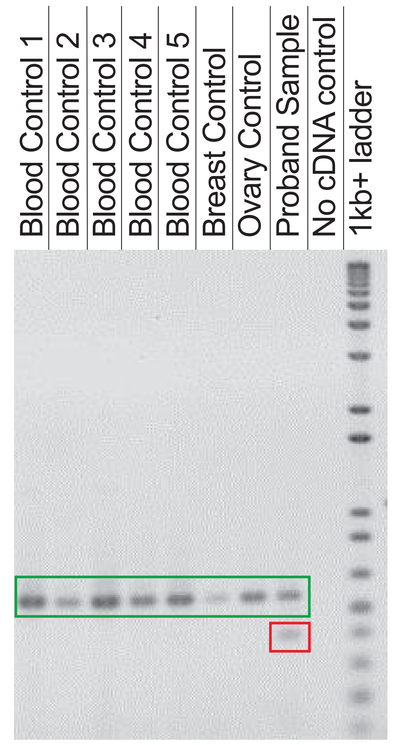


Table 1. Clinical Summary of the Biallelic BRIP1 Mutation Carriers

Clinical Variable	Proband	Brother
Age	67	59
Cancer History	Breast cancer at age 64	None
Genotype	+ / +	+ / +
CBA	Positive	Positive
Height	5'4"	5'10"
Reported Clinical Presentation	• No congenital abnormalities, malignancies, or hematological issues prior to breast cancer diagnosis • Unusually severe hematologic toxicity in response to chemotherapy	• No skeletal abnormalities, malignancies, or hematological concerns

CONCLUSIONS

- The proband and her brother had a genetic and molecular diagnosis of Fanconi Anemia; however, their clinical presentation is inconsistent with previously reported cases of FANCJ.
- This suggests that the phenotypic spectrum of FANCJ is wider than previously reported and that relying on clinical diagnosis of Fanconi Anermia may be insufficient. This has implications for the use of *in trans* co-occurrences to establish the pathogenicity of variants.
- The increased clinical use of hereditary cancer panels that include multiple genes associated with Fanconi Anemia may continue to expand our knowledge of atypical presentations of Fanconi Anemia due to *BRIP1* and other genes.

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