Lower Penetrance Germline Fanconi Anemia Variants in Breast Cancer: Opportunities for Expanded Genetic Testing and Therapeutic Targeting in the Updated INSPIRE Study Cohort

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BACKGROUND

- Disruption of the Fanconi Anemia (FA) DNA repair pathway can impair homologous recombination (HR).
- High-penetrance monoallelic pathogenic/likely pathogenic (PLP) variants in *BRCA1* (*FANCS*), *BRCA2* (*FANCD1*), and *PALB2* (*FANCN*) are well-known breast cancer susceptibility genes contributing to HR deficiency (HRD).
- The clinical impact of germline monoallelic PLP variants in other, non high-penetrance (non-HP) FA pathway genes remains unclear.
- Invasive breast cancer (IBC) is common, affecting 12-13% of average-risk women.
- Targeted therapies and precision medicine offer opportunities for improved outcomes.
- Findings could inform HRD-related precision therapies and influence clinical trial eligibility.

METHODS

- This retrospective study included consented patients with IBC enrolled in the City of Hope INSPIRE Study as of January 14, 2025.
- Germline sequencing of 155 cancer predisposition genes was performed.
- Patients with multiple FA variants were classified by the gene with the highest penetrance.
- A subset of the cohort underwent paired tumor-normal whole exome sequencing (WES) with high coverage (>400x tumor, >180x normal).
- HRD scar scoring, mutational signatures, and loss of heterozygosity were assessed to determine effects on HR integrity.
- Clinical data were obtained from cancer registries and medical records.

The clinical impact of germline monoallelic PLP variants in non-HP FA pathway genes remains unclear.

RESULTS

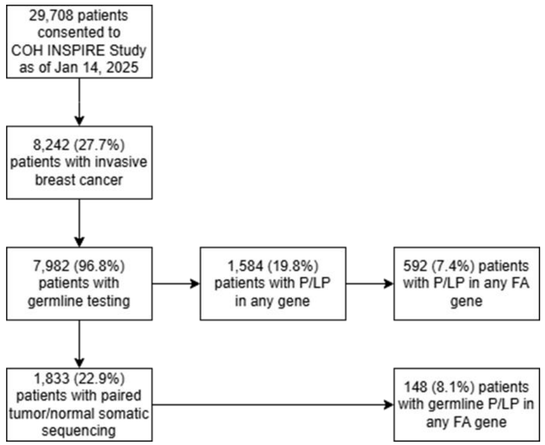


Figure 1: Consort diagram

- Of 8,242 patients with IBC, 7,982 had germline sequencing; 592 (7.4%) carried an FA gene PLP variant.
- Stage data (n=1,548): 128 (8.3%) patients were diagnosed with stage IV IBC of which 7/128 (5.5%) had non-HP FA PLP variants

RESULTS CONT.

Gene	Pts with germline P/LPs n (% of total, N=1,833)		HRD score ≥ 42
Highly Penetrant BC Predisposition FA Genes			
BRCA2 (FANCD1)	92 (5.02%)	47 (2.56%)	39 (81.25%)
BRCA1 (FANCS)		30 (1.64%)	26 (86.67%)
PALB2 (FANCN)		15 (0.82%)	13 (86.67%)
Other FA Genes			
FANCA	53 (2.89%)	14 (0.76%)	4 (28.57%)
FANCM		13 (0.71%)	6 (46.15%)
BRIP1 (FANCJ)		7 (0.38%)	5 (71.4%)
FANCC		3 (0.16%)	2 (66.7%)
FANCD2		2 (0.11%)	0 (0.0%)
ERCC4 (FANCQ)		2 (0.11%)	1 (50.0%)
SLX4 (FANCP)		3 (0.16%)	0 (0.0%)
FANCG		2 (0.11%)	2 (100.0%)
FANCI		2 (0.11%)	1 (50.0%)
FANCF		1 (0.05%)	1 (100.0%)
FANCL		3 (0.16%)	2 (66.7%)
FANCE		1 (0.05%)	0 (0.0%)
RAD51C (FANCO)		0 (0.00%)	NA
FANCB		0 (0.00%)	NA

Figure 2: Germline P/LP rates and Molecular features of patients with IBC with P/LP Variants in FA genes from COH-INSPIRE (N=1,833)

- Among FA variants, 197 (33.3%) were in non-high-penetrance (non-HP) FA genes.
- In 1,833 patients with paired tumor-normal sequencing, 145 (7.9%) had an FA PLP variant; 53 (2.9%) were non-HP.
- 45.3% (24/53) of non-HP FA variant carriers had HRD-positive tumors (HRD score ≥42).
- Non-HP FA variant carriers were more likely to have HRD-positive tumors than non-carriers (RR 1.51, 95% CI 1.12–2.05; p < 0.0077).

CONCLUSIONS

- Non-HP FA gene PLPs are common in patients with IBC.
- Non-HP FA gene-altered tumors have elevated HRD scores compared to non FA gene-altered tumors. These variants may affect cancer biology and function.
- Most common non-HP FA gene variants occurred in *FANCA* and *FANCM* (recurrent variants c.5791C>T and c .5101C>T)
- These results supports broader germline testing beyond the known high-risk genes.
- Trial eligibility should include more FA pathway genes.
- Non-HP FA variants may help identify patients for HRD-targeted therapies.

Non-HP FA gene PLPs are common in patients with IBC and affect cancer biology.

FUTURE DIRECTIONS

- Gene-level and allele-specific loss of heterozygosity (LOH) in FA genes
- Subgroup analysis of non-HP FA carriers (clinical characteristics and outcomes)

REFERENCES

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