BRCA1 frameshift variants leading to extended incorrect protein termini

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- Moffitt Cancer Center and Research Institute
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Presenter Disclosure

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Speakers Bureau/Honoraria:
n/a

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n/a
Learning Objective

At the conclusion of this presentation, participants will be able to:

Understand that BRCA1 extended incorrect termini variants must be evaluated and interpreted on a case-by-case basis
Extended Incorrect Termini (EIT) variants

Wild-type: ATA CCC CAG ATC CCC CAC AGC CAC TAC TGA CTG CAG CCA GCC ...
          IPQ IP HSHY *

EIT:    ATA CCC CAG ATC CCC CCA C AGC CAC TAC TGA CTG CAG CCA GCC ...
          IPQ IP PQLLTLTAAS ...
Functional assays to probe BRCA1 function

Transcriptional activation

Family History (FHx) modeling

BRCA1 EIT variants

HDR assay

Protein-protein interaction

05/02/23
Documented EIT variants in BRCA Exchange
Transcriptional activation
EIT variants selected for additional analysis

c.5578dup +2 ....PQPLLTAASHRYRATGPQE
c.5578del +3 ....-----TATTDQSQPQVQSHTRPRMSLQSGLSRPWELLSLFSPSTVLATKYPMYISLKRRTSGYARVP
c.5579*2del16 +3 ....--------RSQPQVQSHTRPRMSLQSGLSRPWELLSLFSPSTVLATKYPMYISLKRRTSGYARVP
Protein-protein interactions

**Diagram:**
- BRCA1
- ABRAXAS
- PALB2
- BRIP1

**Table:**

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<tr>
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<th>Vector</th>
<th>WT BRCA1</th>
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**Blots:**
- BRCA1 (α-myc)
- PALB2
- BRIP1
- ABRAXAS
- IgG HC

**Lanes:**
- Lanes 1-6: WCE
- Lanes 7-12: anti myc IP
Homology-directed repair

![Graph showing % HR activity for different conditions]
Family History (FHx) modeling

LLR = -4.16

24 carriers of c.5578dup
Conclusions

1. Most frameshift changes that produce EIT are likely to lead to loss of function

2. The c.5578dup variant is likely to produce functional protein

3. Our data highlight the need for individual characterization of these EIT variants
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