Towards massively parallel translation

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The University of Melbourne
For almost two decades the heritable cause of breast cancer susceptibility has been identified in the vast minority of women.
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**Genetic Breast Cancer Susceptibility**

**Translated**

**Gene Discovery**

**Basic Research**
- International breast cancer linkage study
- Whole exome/genome sequencing

**Translation**
- Evidence-based translation of new genetic information

**Clinical Genetics Practice**

**Early-onset cases with a strong family history**

**Missing heritability**

BRCA1
BRCA2
PALB2
CHEK2
ATM
TP53
**PALB2 (FANCN)**

- PALB2 (partner and localiser of BRCA2) was discovered as a protein that interacts with BRCA2.

- PALB2 co-localises with BRCA2 and promotes its nuclear localisation and stability. This in turn facilitates the function of BRCA2 in homologous recombination and double-strand break-repair.

- Biallelic mutations in PALB2, similar to biallelic BRCA2 mutations, cause Fanconi anemia.

- BRCA1 associates with BRCA2 via PALB2

- Palb2 synergizes with Trp53 to suppress mammary tumour formation

- First reported as a breast cancer susceptibility gene in 2007.

\[\text{(D) A working model of the BRCA1/BRCA2/PALB2 complex in the DNA damage response.}\]

*Sy et al., PNAS 2009*
The Australian Breast Cancer Family Study is a population-based case-control-family study.

767 women diagnosed with breast cancer before the age of 40 years were recruited between 1992 and 1999.
The Australian Breast Cancer Family Study

No affected relatives

One affected relative

Two or more affected relatives

x BRCA2 mutation carriers (n=22)

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The Australian Breast Cancer Family Study

- No affected relatives
- One affected relative
- Two or more affected relatives

x BRCA2 mutation carriers (n=22)

Towards massively parallel translation
The Australian Breast Cancer Family Study

<table>
<thead>
<tr>
<th>Number of Affected Relatives</th>
<th>BRCA2 Mutation Carriers (n=22)</th>
<th>PALB2 Mutation Carriers (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>One</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>No</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Towards massively parallel translation
PALB2, c.3113G>A (W1038X)

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PALB2, c.3113G>A (W1038X)
**PALB2, c.3113G>A (W1038X)**

Towards massively parallel translation
Mutations in *PALB2* are rare, but far more common in breast cancer cases with a strong family history than in unaffected population-based controls.

<table>
<thead>
<tr>
<th>PALB2 mutations</th>
<th>Case-carrier frequency</th>
<th>Control-carrier frequency</th>
<th>Reference</th>
<th>“Study Design”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/747</td>
<td>-</td>
<td>Teo et al 2013a</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td><em>PALB2</em> c.3113G&gt;A, p.Trp1038*</td>
<td>1/70</td>
<td>-</td>
<td>Wong et al 2011</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td></td>
<td>5/1403</td>
<td>0/764</td>
<td>Southey et al 2010</td>
<td>Population-based</td>
</tr>
<tr>
<td></td>
<td>2/66</td>
<td>-</td>
<td>Southey et al 2010</td>
<td>Early-onset multiple-case</td>
</tr>
<tr>
<td></td>
<td>8/871</td>
<td>-</td>
<td>Teo et al 2013b</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td></td>
<td>7/747</td>
<td>-</td>
<td>Teo et al 2013a</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td><em>PALB2</em> c.2235delA, p.Lys745Lysfs*19</td>
<td>1/680</td>
<td>-</td>
<td>-</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td><em>PALB2</em> c.1685-2A&gt;G</td>
<td>1/680</td>
<td>-</td>
<td>-</td>
<td>Familial breast cancer</td>
</tr>
<tr>
<td><em>PALB2</em> c.2982_2983insT, p.Ala995fs*16</td>
<td>1/747</td>
<td>-</td>
<td>Teo et al 2013a</td>
<td>Familial breast cancer</td>
</tr>
</tbody>
</table>

It is difficult to use the cancer histories of these families to make informative estimates of risk (penetrance) when the reason for studying them has been their family cancer history.

Inference is more informative when based on testing families unselected for family history, but there is a paucity of such data for these genes.

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Segregation analyses of the population-based families that carry the PALB2 c.3113G>A (1038X) mutation.

- First and second degree relatives
- Mixed model (polygenic background plus *PALB2* major gene)

**Hazard ratio (HR) estimate of 30.1 (95% CI 7.5 – 120; p<0.0001)**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Penetrance to age (Age)</th>
<th>Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2 c.3113G&gt;A</td>
<td>50</td>
<td>49% (15-93)</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>91% (44-100)</td>
</tr>
<tr>
<td>ATM c.7271T&gt;G</td>
<td>70</td>
<td>52% (28-80)</td>
</tr>
<tr>
<td>PALB2 c.1592delT</td>
<td>70</td>
<td>40% (17-77)</td>
</tr>
<tr>
<td>BRCA2 (average)</td>
<td>70</td>
<td>45% (31-56)</td>
</tr>
</tbody>
</table>

Southey 2010

ATM c.7271T>G  penetrance to age 70  52% (95%CI 28-80)  
Bernstein 2006

PALB2 c.1592delT  penetrance to age 70  40% (95%CI 17-77)  
Erkko 2008

BRCA2 (average)  penetrance to age 70  45% (95%CI 31-56)  
Antoniou 2003

Population-based family studies have shown that some mutations in “moderate risk” genes are associated with a substantially increased risk of breast cancer.

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PALB2 Interest Group

154 families, including 362 individuals
Deleterious truncating, splice, or deletion mutations in \textit{PALB2}.
Age-specific breast cancer risks for mutation carriers were estimated

The estimated cumulative risk
- 14\% (95\%CI: 9\%-20\%) by age 50
- 35\% (95\%CI: 26\%-46\%) by age 70.

The absolute risk by age 70 ranged from
- 33\% (95\%CI: 25\%-44\%) for those with no family history, to
- 58\% (95\%CI: 50\%-66\%) for those with two or more first-degree relatives
  with young-onset breast cancer.


Towards massively parallel translation
## iCOGS:
Summary results from studies of white Europeans

<table>
<thead>
<tr>
<th>VARIANT</th>
<th>Controls (Frequency)</th>
<th>Cases (Frequency)</th>
<th>OR (95%CI)</th>
<th>p-value LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALB2 W1038X</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>13,484 (0.00019)</td>
<td>14,769 (0.00101)</td>
<td>5.93 (2.77-12.7)</td>
<td>6.9x10⁻⁸</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>8,330 (0.00120)</td>
<td>9,774 (0.00061)</td>
<td>0.50 (0.18-1.38)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>10,151 (0.00079)</td>
<td>4,967 (0.00101)</td>
<td>1.34 (0.36-4.97)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>PALB2_1529delT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>13,484 (0.00014)</td>
<td>14,769 (0.00082)</td>
<td>4.52 (1.90-10.8)</td>
<td>7.1x10⁻⁵</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>8,819 (0.00045)</td>
<td>9,309 (0.00075)</td>
<td>2.06 (0.60-7.14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>2,374 (0.00042)</td>
<td>2,078 (0.00096)</td>
<td>2.50 (0.21-29.1)</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Until recently there have been few agreed guidelines in the hereditary cancer field in Australia and none regularly updated - essential in this rapidly progressing field.
eviQ Cancer Treatments Online:

2000
Prof Robyn Ward developed the eviQ point of care guidelines for cancer treatments to provide accurate, current, relevant and evidence based information for use at the point of care.

The eviQ site hosts more than 1,300 evidence based protocols and content items relevant to clinical practice.

2008
Cancer genetics became a component of the eviQ cancer management guidelines: NSW focus

2011
Interest from the wider Australian familial cancer community resulted in the extension of the eviQ reference committee to include nominees from all states of Australia.

eviQ is now established as a national platform to host point of care information of great relevance to the practice of cancer genetics.

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Missing heritability

Early-onset cases with a strong family history

BRCA1
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TP53

Gene Discovery

Gene Panel Testing

Clinical Genetics Practice

Translation
Evidence-based translation of new genetic information

Towards massively parallel translation

1. Responsive to accumulating the evidence for translation
2. Define and enable a pathway for “massively parallel translation”
Research Resources:

Australian Breast Cancer Family Study
Breast Cancer Family Registry (NCI, USA)
kConFab

Funding:

National Health and Medical Research Council
Project Grant: Southey, Goldgar, Winship
*Translation of PALB2 Genetic Information Into Breast Cancer Clinical Genetic Services*
European Union Health Collaborative Research Grant
*Collaborative Oncological Gene-Environment Study*

National Breast Cancer Foundation
National Institute of Health, USA,
Victorian Cancer Council
Susan G. Komen for the Cure
Cancer Australia
Victorian Breast Cancer Research Consortium

eviQ
Cancer Council NSW
Cancer Institute NSW

Towards massively parallel translation
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University of Melbourne and Royal Melbourne Hospital

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Huntsman Cancer Institute,
University of Utah School of Medicine, SLC, Utah

A/Professor Judy Kirk
Director, Familial Cancer Service Westmead Hospital
(Chair, eviQ cancer genetics reference committee).

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