Unknown genetic predisposition in familial breast cancer can lie deep in family tree

San Ming Wang
University of Nebraska Medical Center
Genetically defined breast cancer

• Sporadic Breast Cancer caused by somatic mutation
  90% of breast cancer – “bad luck”
• Familial Breast Cancer caused by germline mutation
  10% of breast cancer - inherited

http://www.cancer.gov/types/breast
In 1866, French physician Paul Broca reported 10 women over four generations in his wife’s family died from breast cancer.
Genetic predisposition is the major factor for familial breast cancer

- Factors contributing to cancer include environment, lifestyle, nutrition, infection, genetics etc.
- Genetic predisposition is considered as the major factor responsible for familial breast cancer
- Familial breast cancer is a genetic disease
**BRCAx familial breast cancer**

- Germline mutations in *BRCA1 and BRCA 2 genes* are known genetic predispositions for familial breast cancer.
- Germline mutations in *BRCA1 and BRCA 2 genes* are present in 10-20% of familial breast cancer.
- Predispositions for 40-50% of FBC are known.
- Predispositions for 50-60% of FBC remain unknown.
Efforts made to identify the unknown predispositions

- linkage analysis, positional cloning, genomic arrays, targeted sequencing, GWAS, exome sequencing have been applied
- Large sample sizes of tenth of thousand cases per study are routinely used
- Newly identified predispositions are very limited
Newly identified predisposition are all rare

<table>
<thead>
<tr>
<th>Predisposition</th>
<th>BC cases</th>
<th>BC cases with mutation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRCC2</td>
<td>3,371</td>
<td>5</td>
<td>Park et al, 2012</td>
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<tr>
<td>XRCC2</td>
<td>3,548</td>
<td>0</td>
<td>Hilbers et al, 2012</td>
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<tr>
<td>FANCC</td>
<td>1,435</td>
<td>1</td>
<td>Tompson et al, 2012</td>
</tr>
<tr>
<td>BLM</td>
<td>1,435</td>
<td>4</td>
<td>Tompson et al, 2012</td>
</tr>
<tr>
<td>BRIP1/BACH1</td>
<td>357</td>
<td>2</td>
<td>Cao et al. 2010</td>
</tr>
<tr>
<td>PPM1D</td>
<td>6,634</td>
<td>21</td>
<td>Ruark et al.</td>
</tr>
<tr>
<td>Total</td>
<td>16,789</td>
<td>33 (0.5%)</td>
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</tbody>
</table>
The rarity makes it indistinguishable between disease and normal population


- The same mutation failed to be detected in another 3,548 BRCA1/2-negative familial breast cancer cases but in 1 of 1,435 normal control (Hilbers et al. J Med Genet. 49(10):618-20, 2012)
Current theory to explain germline predispositions in familial breast cancer

- **High-risk genes**: rare mutations convey high-risk, such as *BRCA1*;
- **Intermediate-risk genes**: rare mutations convey intermediate risk, such as *CHEK2*;
- **Modest risk genetic variants**: common genetic variants such as the SNPs detected by GWAS population studies.
Distribution of known genetic predispositions

Fanale et al. Oncogene 31(17):2121-8, 2012
Question: frequency of unknown predispositions

![Graph showing allele frequency and relative risk for different genetic markers.]

- **BRCA1/2**
- **P53**
- **PTEN**
- **CHEK2, PALB2, ATM, BRIP1**
- **FGFR2, LSP1, MAP3K1, 2q35, 8q, 6q**

Existing?
Hypothesis:
Unknown predisposition can be family-specific

• FBC is an autosomal dominant disease
• Each family is enriched with the predisposition
• Focus on family may have higher chance to identify the unknown predisposition than population screening (diluted)
Studies in *BRCAx* families
Exome sequencing

- Next-generation sequencing-based
- >180,000 exons from around 20,000 genes in the human genome
- 1/100 genome DNA content
- 1/5 cost of sequencing whole genome ($1,000)
- 85% of known genetic diseases are caused by mutation in exon!
Germline mutations in three *BRCA* families are highly family-specific
Putative genetic predisposition in each *BRCAx* family

<table>
<thead>
<tr>
<th>Gene</th>
<th>Position</th>
<th>Change</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>PINK1</td>
<td>chr1:20972051</td>
<td>-2A&gt;G</td>
<td>- + + - - - -</td>
</tr>
<tr>
<td>USP28</td>
<td>chr11:113683049</td>
<td>A&gt;G</td>
<td>- + + - - - -</td>
</tr>
<tr>
<td>TIGD2</td>
<td>chr4:90034310</td>
<td>C&gt;T</td>
<td>- - - - + +</td>
</tr>
<tr>
<td>KAT6B</td>
<td>chr10:76789128</td>
<td>G&gt;T</td>
<td>+ + + + + +</td>
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<tr>
<td>KAT6B</td>
<td>chr10:76789311</td>
<td>C&gt;T</td>
<td>+ + + + + +</td>
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<tr>
<td>NOTCH2</td>
<td>chr1:120459167</td>
<td>C&gt;T</td>
<td>+ - - - - +</td>
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<tr>
<td>ADCY9</td>
<td>chr16:4016224</td>
<td>G&gt;A</td>
<td>+ - + - - -</td>
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<td>PHKB</td>
<td>chr16:47628126</td>
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<td>+ - - + - -</td>
</tr>
<tr>
<td>NANP</td>
<td>chr20:25596725</td>
<td>A&gt;G</td>
<td>- + + - - -</td>
</tr>
<tr>
<td>PPP6R2</td>
<td>chr22:50857867</td>
<td>C&gt;A</td>
<td>- - - + + +</td>
</tr>
</tbody>
</table>
$KAT6B$

$KAT6B$ gene structure

$KAT6B$ protein domains

chromatin targeting

H1/5  PHD  MYST  ED

 Activation

Ser rich  Met rich

1

2073

G>T
p.D1516Y

C>T
p.R1577C

RUNX1/2 interaction
**KAT6B**

- A histone acetyl-transferase
- Its N-terminal is involved in transcriptional repression while its C-terminal is involved in transcriptional activation
- Interacts with important transcriptional regulators RUNX1 and RUNX2.
- A component of the MOZ/MORF complex involved in DNA replication, transcriptional regulation, and epigenetic modification of chromatin structure
- Mutations cause several neural genetic disease
- Not known involved in familial breast cancer
Are the same germline mutations in KAT6B also present in other BRCA\(x\) families?

- 42 additional cancers from 26 BRCA\(x\) families were tested
- None of the mutations are present in these families
- Sequencing entire \textit{KAT6B} gene see no mutations
Distribution of germline mutations in 26 BRCAx families
Each *BRCAx* breast cancer family may have its own genetic cause.

Familial-specific predisposition

![Diagram showing relative risk and allele frequency for different genes involved in breast cancer predisposition.](image-url)
Genetic predispositions in familial breast cancer: Same Disease, Different Causes

- Common predispositions only exist in a portion of familial breast cancer
- Family-specific predispositions are responsible for many familial breast cancer
- Family-based approach can identify the unknown predispositions
- Precision medicine, personalized medicine, familial medicine….

Wen et al. BMC Cancer. 2014;14:470
Contribution

University of Nebraska Med Center
  Yeong C. Kim
  Bradley Downs
  Hongxiu Wen
  Fengxia Xiao
  Peixian Chen
  Jiangtao Luo
  San Ming Wang

Creighton University
  Carrie Snyder
  Mark Stacey
  Dina Becirovic
  Henry Lynch