Genetics of cancer in EGAT study

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• Cancer develops because of a complex mix of environmental and genetic factors.

• For some:-
  – Environmental factors pose the greatest risk

• For others:-
  – It is inherited susceptibility

• For most:-
  – Combination of all the above.
The leading sites of cancer in Thailand
Ministry of Health 2005
Etiology of Cancers

- Hereditary: 5%
- Familial: 20%
- Sporadic: 75%
The Cell Cycle

- **M** (mitosis)
- **G₀** (resting)
- **G₁** (cell growth)
- **S** (synthesis)
- **G₂**

**Key Points:****
- Oncogenes
- DNA repair genes
- Tumor suppressor genes

- **Stop** sign indicating a halt in the cycle.
- **Repairs Ahead** sign indicating DNA repair genes in the cell cycle.
Cancers Arise From Gene Mutations

in genes protecting **against** cancer

tumour
All cancer is genetic

BUT

not all cancer is inherited!
Most Cancers Arise From Somatic Mutations

- Somatic mutation
  - Localised to a specific tissue
    - Not in germline tissues
    - Not inherited

breast
or
bowel
Knudson’s ‘Two-Hit Hypothesis’
(Somatic Mutation)

First hit

Second hit

tumour
5-10% of Cancers Arise From Germline Mutations

- Germline mutation
  - In egg or sperm
  - May be passed on (inherited)
  - All cells in offspring carry the mutation
Knudson’s ‘Two-Hit Hypothesis’
(Germline Mutation)

First hit is in germline

Second hit is somatic

Tumour
Multi-Step Carcinogenesis (eg, Colon Cancer)

Loss of APC

Activation Loss of K-ras 18q Loss of TP53 Other alterations

Normal epithelium → Hyper-proliferative epithelium → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma → Metastasis

Adapted from Fearon ER. Cell 61:759, 1990
The Cell Cycle

M (mitosis) → G1 (cell growth) → S (synthesis) → G2 → G0 (resting)

Oncogenes

DNA repair genes

Tumor suppressor genes
1. **Tumor suppressor genes:**

   The cell’s brakes for tumor growth

   ![Diagram](image-url)
Genes Associated With Cancer

2. Oncogenes:
   accelerate cell division

1 mutation sufficient for role in cancer development
In summary...
Examples of hereditary cancer genes

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<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Disorder</th>
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<tr>
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<td>SDHA/B/C</td>
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<td>HNPCC</td>
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<td>PTEN</td>
<td>Cowdens syndrome</td>
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## Pattern of cancer

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<th>Skin</th>
<th>GI tract</th>
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<th>Female genital tract</th>
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Population of EGAT study

- EGAT 1 ~ 2,800
- EGAT 2 ~ 2,200
- EGAT 3 ~ 2,000

Cancers ~ 480
Half of the population have had a 1st or 2nd degree relative diagnosed with cancer
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Half of the population have had a 1st or 2nd degree relative diagnosed with cancer.

2nd degree (grandparents, aunts, uncles, nieces, nephews)
Half of the population have had a 1st or 2nd degree relative diagnosed with cancer

Only 5% - 10% will have an inherited genetic factor
1. Deletion or Point Mutation in Coding Sequence: constitutively active protein produced in normal amounts.

2. Gene Amplification: normal protein produced in much higher amounts.

3. Chromosome Rearrangement:
   a) placement of strong enhancer nearby causes overproduction of normal protein.
   b) fusion to another actively transcribed gene results in either increased levels of the fusion product (normal activity overproduced) or the fusion protein is hyperactive (increased activity in normal amounts).
Illumina technique
Outcome Prediction

1. Identified group of cancer genes in EGAT population
2. Identified individual ‘s risk for cancer prevention
3. Apply these genetic markers to Thai population
4. Appropriate surveillance screening
5. Compromise health economics
Gene mutations and inherited cancer
How are cancer predispositions inherited?
Hereditary Breast Cancer (high risk)

- ~5% of all Breast Cancers
- Monogenetic disorder
- Autosomal dominant inheritance
- High penetrance
- Early onset
- Cancer syndrome (other cancers also)
- BRCA1+2 only known genes of major importance
Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- Equally likely to affect males and females
- No “skipped generations”
- Equally transmitted by men and women

Diagram:
- Squares represent normal males.
- Circles represent normal females.
- Black squares represent affected males.
- Black circles represent affected females.
- White squares represent normal males.
- White circles represent normal females.
Penetrance

May appear to “skip” generations

Individuals inherit altered cancer susceptibility gene - not cancer
Factors Affecting Penetrance

Modifier genes

Response to DNA damage

Carcinogens

Hormonal/reproductive factors

Not everyone with an altered gene develops cancer
Age-Specific Penetrance

Affected with colorectal cancer (%)

Age in years

Modified from Aarnio M et al. *Int J Cancer* 64:430, 1995
High Risk Indicators

- Multiple family members with tumours at same site
- Early age of onset
- History of individuals with multiple primary tumours
- Recognised associations:
  - Breast/ovary
  - Bowel/Endometrium
  - etc.
Breast Cancer
NICE - familial breast cancer

*Mammographic surveillance*

**High risk:**

- 30-40 *individualised strategies*
  - Mammography or MRI?

**40-50 annual**

**50+ *individualised strategies***
FAP
Genetics of FAP

- Caused by mutations in APC gene (found on chromosome 5)

- ~30% occur as the result of new mutations

- Correlation between position of mutation &:
  - Severity of effect
  - Presence of CHRPEs and desmoids
FAP: Key Points

- CRC risk is 100% in untreated FAP patients
- Genetic testing identifies most APC mutation carriers
- Endoscopic surveillance and prophylactic colectomy can improve survival in at-risk patients
- Non-carriers can be spared anxiety and the need for increased surveillance
Family History is the key to diagnosing HNPCC

CRC dx 50s

CRC dx 45
CRC dx 48
CRC dx 42
CRC dx 52
CRC dx 59
CRC dx 75
CRC dx 64
Endometrial Ca, dx 59
45
Genetic Features of HNPCC

- Autosomal dominant inheritance
- Penetrance ~80%
- Genes belong to DNA mismatch repair family
- A number of genes involved
  \((MLH1, MSH2, MSH6, PMS1, PMS2)\)
Amsterdam Criteria

- 3 or more relatives with CRC
- One case a 1st degree relative of the others
- Two or more generations
- One CRC by age 50
- FAP excluded

Modified Amsterdam criteria: An endometrial cancer can be substituted for one of the CRC
Taking a Pedigree
Drawing up the family tree gives information about the relatives and also:

• helps establish the family agenda and dynamics

• may reveal individuals' interpretation and beliefs about what is happening in the family

• Has the potential to raise issues of paternity
Start with the couple being seen

Use clear symbols: circles for females, squares for males

The horizontal line denotes a relationship (males usually on the left, females on right)

Add in their children

The vertical line denotes offspring of the relationship

“Have you had any children with other partners?”

Record names, dates of birth
Choose one parent and ask about:
brothers and sister and their children
parents and grandparents
Make sure you ask about ethnicity
Joyce Jones 22.9.46
Stephen Jones 12.10.42 30.4.86
Catherine 12.2.46
Emma 30.9.73
Paul Jones 7.4.70
Sarah Barclay 5.5.73
Kieran 11.4.95
Ann Brown 29.9.48

Add the age at which diagnosis was made
Put a sloping line through the symbol (from the bottom left hand corner) if the person has died

Colour in the symbol if the person is affected
88

Peter Jones
28.4.1884
d 23.09.1974

Edith
17.10.1887
3.7.1965

Herbert Jones
29.9.14
d 8.6.03

Gertrude
24.11.20

Joyce Jones
22.9.46

Stephen Jones
12.10.42
30.4.86

Catherine
12.2.46

Paul Jones
7.4.70

Sarah Barclay
5.5.73

Emma
30.9.73

Kieran
11.4.95

Thomas Phillips
10.9.07

Mary
3.1.10
17.6.63

Ann
Brown
29.9.48

Key:
- Ca lung
- Ca colon

Use a key if more than one form of cancer
Add information on the other side of the family
Other pedigree symbols

- Double line joins union of consanguineous couple
- Double line indicates that relationship has ended
- Pregnant
- Twins: identical; non-identical
- 4 unaffected persons whose sex is unknown
- No offspring
Drawing a pedigree

Pedigree Template
One of the resources available from the NHS National Genetics Education and Development Centre
www.geneticseducation.nhs.uk

Resource database
- Existing resources
- Resources developed by the Centre

Searchable
- Search all
- Linked to educational outcomes

Evaluated

3. Be able to identify patients with, or at risk of, a genetic condition
   - Be able to take a family history and construct and interpret a pedigree
Genes Associated With Cancer

3. DNA damage-response genes: the repair mechanics for DNA

![Diagram showing DNA repair process]
DNA damage-response genes:

Base pair mismatch

Mutation introduced by unrepaired DNA