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Loss of heterozygosity on 22q
and KIT gene mutations
in Gastrointestinal Stromal Tumors (GIST)

(Agnieszka Woźniak, PhD,
Bartosz Wasąg, MSc)
Gastrointestinal stromal tumors (GIST)

- rare mesenchymal tumors of gastrointestinal tract

Localisation:
- 70% - stomach
- 20-30% - small intestine
- <10% - esophagus, colon, rectum
Immunochemistry

The expression of c-kit protein (CD117) is the best defining feature of GISTs and is seen in nearly all cases.
Aims of the study

• Finding most commonly deleted region of 22q in Gastrointestinal Stromal Tumors

• Describing the frequency and type of KIT gene mutations in GISTs
Loss of genetic material from chromosome 22q in GISTs
KIT gene

- **Localisation:** 4q12
- **21 exons; 34kb**
- **Coding transmembrane tyrosine kinase receptor for a stem cells factor (SCF)**
- **Expression:**
  - germ cells
  - stem cells
  - melanocytes
  - intestinal cells of Cajal
**KIT mutations in GISTs**

<table>
<thead>
<tr>
<th>Exon</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
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<tbody>
<tr>
<td></td>
<td>EC</td>
<td>TM</td>
<td>JM</td>
<td>TK1</td>
<td>KI</td>
<td>TK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Exon 9: 1530ins6 (GCC TAT)**
- Duplication of Ala<sup>502</sup> and Tyr<sup>503</sup>

**Exon 11: Deletions, point mutations, insertions**

**Exon 13: Point mutation**
- 1945A>G results in substitution of Glu<sup>642</sup> to Lys
Imatinib (Glivec®): Background

- A selective tyrosine kinase inhibitor of:
  - BCR-ABL
  - PDGFRA
  - KITC
- First used in Philadelphia chromosome–positive (Ph+) CML
  - Target BCR-ABL
Imatinib and GIST: $^{18}$FDG-PET Scan

Multiple liver and upper abdominal $^{18}$FDG-accumulating metastases

A marked decrease in $^{18}$FDG uptake 4 weeks after starting imatinib

CT Scan Results: Decrease in Tumour Volume

June 27, 2000
Before imatinib

October 4, 2000
After imatinib

Novartis GIST Conference, London, UK, 2002
“BRCA 1 and BRCA2 mutation analysis in breast-ovarian cancer families from north-eastern Poland”

(Magdalena Perkowska, MSc)
Susceptibility to breast and ovarian carcinoma is inherited by the transmission of an autosomal dominant allele in approximately 3% of breast cancer and in 5-10% of all ovarian cancer cases.

Genetic transmission of mentioned factor was first reported in the early 1970s.

Two major suppressor genes associated with hereditary breast and ovarian carcinoma have been identified, BRCA1 and BRCA2.

Germline mutations in BRCA1 (17q12-21) are associated with an increased risk of breast and ovarian cancer in females. The risk of developing an invasive breast carcinoma is estimated approximately 70% by the age of 70 years.

Germline mutations in BRCA2 (13q12-13) confer an increased risk for both female and male breast cancer from 37% to 84% by the age of 70 years.
The purpose of this project is to analyse 200 high-risk breast and/or ovarian cancer families from north-eastern Poland for mutations in the BRCA1 and BRCA2 genes.

Mutation screening is being performed with a combination of screening techniques such as DHPLC and PTT and direct sequencing of all coding exons in BRCA1 and BRCA2 genes.
PTT - Protein Truncation Test is used in screening for frameshift and nonsense mutations in BRCA1 ex 11 and BRCA2 ex 10 and 11.

* The arrow points an extra band corresponding to shorter translation product.

DHPLC - Denaturing High Performance Liquid Chromatography is used in screening for mutations and polymorphisms in all coding BRCA1 and BRCA2 exons (despite of those analysed by PTT).

* The arrow points an extra pick corresponding to heteroduplex.
Until now the screening for mutations in BRCA1 and BRCA2 genes was completed for the group of 60 high-risk families.

The analysis results are presented in the table.
Table 1: BRCA1 and BRCA2 Mutations Identified in the Present Study of 60 Breast Cancer Families from North-Western Poland

<table>
<thead>
<tr>
<th>No.</th>
<th>Exon no.</th>
<th>Nucleotide change</th>
<th>Effect</th>
<th>Mutation type</th>
<th>Mutation status</th>
<th>Proband status (age)</th>
<th>Family type</th>
<th>Family no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>185delAG</td>
<td>FS; ter 39</td>
<td>F</td>
<td>founder</td>
<td>Brea (55)</td>
<td>Br</td>
<td>brea_1</td>
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<tr>
<td>2.</td>
<td>5</td>
<td>300T&gt;G</td>
<td>Cys61Gly</td>
<td>M</td>
<td>founder</td>
<td>Brea (43)</td>
<td>Br</td>
<td>brea_14</td>
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<tr>
<td>3.</td>
<td>5</td>
<td>300T&gt;G</td>
<td>Cys61Gly</td>
<td>M</td>
<td>founder</td>
<td>Ovca (41)</td>
<td>Br/Ov</td>
<td>brea_49/1</td>
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<tr>
<td>4.</td>
<td>5</td>
<td>300T&gt;G</td>
<td>Cys61Gly</td>
<td>M</td>
<td>founder</td>
<td>Brea (46)</td>
<td>Br</td>
<td>brea_54</td>
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<tr>
<td>5.</td>
<td>11</td>
<td>2682C&gt;T</td>
<td>Gln855Ter</td>
<td>N</td>
<td>BIC (4)</td>
<td>Brea (27)</td>
<td>Br</td>
<td>brea_6</td>
</tr>
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<td>6.</td>
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<td>FS; ter 1242</td>
<td>F</td>
<td>recurrent</td>
<td>Ovca (47)</td>
<td>Ov</td>
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<td>7.</td>
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<td>S</td>
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<td>Br/Ov</td>
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<tr>
<td>8.</td>
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<td>5382insC</td>
<td>FS; ter 1829</td>
<td>F</td>
<td>founder</td>
<td>Brea (29)</td>
<td>Br/Ov</td>
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<td>9.</td>
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<td>FS; ter 1829</td>
<td>F</td>
<td>founder</td>
<td>Brea (50)</td>
<td>Br/Ov</td>
<td>brea_19</td>
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<tr>
<td>10.</td>
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<td>Ov</td>
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<tr>
<td>11.</td>
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<td>F</td>
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<td>12.</td>
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<td>13.</td>
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<td>14.</td>
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<td>Ov</td>
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<td>Br</td>
<td>brea_62/2</td>
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</tbody>
</table>

a) Reported in BIC 4 times; families of Western European origin  
b) BIC twice; Spanish/Western Europe origin  
c) BIC once; unknown origin  
d) F: frameshift; M: missense; N: nonsense; S: splice
From the results of the analysis that have been done, we conclude that strong BRCA1 founder effects exist in the Polish population, but also that the BRCA gene mutation spectrum is more dispersed than had been earlier thought. This warrants further careful BRCA mutation scanning in order to optimize genetic counseling and disease prevention in affected families.

We postulate that the BRCA analysis should embrace full gene mutation scanning in selected high-risk families, the main determinants being young age and the presence of ovarian cancer.