Cytogenetics and Forms Completion
or
What language is this???

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What is Cytogenetics?

- Cytogenetics is the study of the structure of chromosome material.
- Chromosomes are genetic structures of cells containing DNA and therefore they:
  * carry inherited traits
  * carry the organization of the cell life
  * heredity-one paternal and one maternal

- Cell life will be disturbed if regular segregation (the separation of homologous chromosomes) fails.
  * During embroyogenesis (constitutional anomalies)
  * In cancer (acquired anomalies)
- The normal human cell is made up of 46 chromosomes:
  * 22 pairs of autosomes, numbered 1-22 by order of decreasing length
  * 1 pair of gonosomes, or sex chromosomes: XX female or XY male
- Each chromosome has a characteristic length and banding pattern
The chromosomes are spread out, fixed and stained to allow examination with a microscope. The cells are then photographed and arranged into a **karyotype** (an ordered set of chromosomes). The karyotype will show the chromosomes of an individual arranged in pairs and sorted according to size.

Diagrams identifying the chromosomes based on the banding patterns are known as **cytogenetic maps**.

Abnormalities are identified by changes in banding patterns along the chromosome.

In some forms of cancer, cytogenetics can determine which chromosomal abnormalities are present in the malignant cells, facilitating diagnosis and treatment.

**Techniques of Analysis**

Routine chromosome analysis refers to analysis of chromosomes which have been banded using trypsin (a serine protease) followed by Giemsa, Leishmanns, or a mixture of the two. This creates a unique banding pattern on the chromosomes. Generally 20 cells are analyzed to rule out chromosome abnormalities.
• Fluorescent in situ hybridization (FISH) is a cytogenetic technique which can be used to detect and localize the presence or absence of specific DNA sequences on chromosomes.
• FISH uses fluorescent probes which bind only to those parts of the chromosome with which they show a high degree of sequence similarity.
• Generally between 200-1000 cells are counted.

Chromosome nomenclature

• Each chromosome has a p and q arm; p (petit) is the short arm and q (next letter in the alphabet) is the long arm. Some of the chromosomes like 13, 14, and 15 have very small p arms. When a karyotype is made, the q arm is always put on the bottom and the p on the top. The arms are separated by a region known as the centromere which is a pinched area of the chromosome.

Karyotype
**Constitutional anomalies**

- All the tissues ("the whole patient") hold the same anomaly. The chromosome error was already present in the embryo.
- "Constitutional anomalies" thus refer to the chromosome inborn syndromes, such as trisomy 21, Turner syndromes, and others.

**Acquired anomalies**

- Only one organ is involved, the other tissues of the body are normal.
- The patient has a cancer of the affected organ. "Acquired anomalies" thus refer to malignancies.

**Mosaic anomalies**

- When only some cells carry the anomaly while others are normal (or carry another anomaly)
- Very common in leukemias and other cancers subject to continuous chromosome change
- In 'ALL' there may be a normal clone, one clone with a specific change, and a third with additional changes (46, XY / 46, XY, t(4;11) / 46, XY, t(4;11), I(7q))
ALL
(46, XY / 46, XY, t(4;11) / 46, XY, t(4;11), i(7q))

Variations in Chromosomal Number

- Euploidy – the normal number and sets of chromosomes
- Polyploidy – the presence of three or more complete sets of chromosomes
- Aneuploidy – the presence of additional or missing individual chromosomes

Types of Polyploidy
- Triploidy – three sets of chromosomes 23 x 3 = 69
- Tetraploidy – four sets of chromosomes 23 x 4 = 92

Types of Aneuploidy
- Monosomy – one less chromosome (23 x 2) – 1 = 45
- Trisomy – one additional chromosome (23 x 2) + 1 = 47
Philadelphia Chromosome (Ph)

- CML is an acquired cytogenetic abnormality that is characterized by the presence of the Philadelphia Chromosome (Ph)
- The Ph chromosome is a result of an exchange of material (translocation) between the long arms of chromosomes 9 and 22 e.g. t(9;22)
- This translocation brings together the BCR gene on chromosome 22 and the ABL gene on chromosome 9
- The resulting hybrid gene BCR/ABL causes uncontrolled cell growth

The t(9;22) translocation
FISH for BCR/ABL

- Fluorescent in situ hybridization (FISH) can determine the presence or absence of a particular segment of DNA — the BCR-ABL gene in the case of CML
- FISH can detect one leukemic cell in 500 normal cells
- FISH results are reported as a CYTO test

Abnormality Types

- add = addition of material of unknown origin
- del = deletion
- de novo = a chromosome abnormality which has not been inherited
- der = derivative chromosome
- dup = duplication
- ins = insertion
- inv = inversion
Abnormalities continued

- Minus sign (-)=loss
- p=short arm of chromosome
- Plus sign (+)=gain
- q=long arm of chromosome
- rea=rearrangement
- t=translocation

Deletion

- Loss of a segment of chromosome
- Invariably, but not always, results in the loss of important genetic material
- In this example the area in the blue brackets is not present (deleted) in its pair designated by the red arrow= **46,XXdel(1)(q24q31)**
- Female with a deletion of chromosome 1 on the long arm (q) between bands q24 to q31.

Duplication

- A duplication is a duplication of a section of a chromosome or three.
- Therefore, if a duplication exists, that person has three copies of that area instead of two.
- This means there are extra instructions (genes) present that can cause an increased risk for birth defects or developmental problems.
In this example, red arrows point to identical bands on each chromosome. The blue arrow points to a duplication of the band at the red arrow. The chromosome on the right is longer.

- **46,XY,dup(7)(q11.2q22)**
- Male with a duplication of chromosome 7 on the long arm (q) between bands 11.2 to 22.

**Balanced Translocation**

- In this example, the long arms of chromosome 7 and 21 have broken off and switched places. There is a normal 7 and 21, and a translocated 7 and 21.
- Recorded as t, followed by a bracket with the numerals of the 2 chromosomes, and a second bracket indicating the presumptive breakpoints e.g. AML. t(15:17)

**Unbalanced Translocation**

- There is an extra copy of 7q and only one copy of 21q. There is extra and missing information creating an 'unbalanced translocation.'
Inversion

- Inversion occurs when a segment of chromosome breaks, and rejoins within the chromosome which effectively inverts it.
- Recorded as $\text{inv}$, followed by a bracket with the number of the chromosome, and a second bracket indicating the breakpoints, where these can be determined (e.g. $\text{inv}(9) (p11q13)$).

Isochromosome

- Loss of a complete arm, “replaced” by the duplication of the other arm.
- Recorded as $i$, followed by a bracket with the number of the chromosome and the arm (e.g. $i(17q)$ or $i(17)(q10)$: duplication of the q arm and loss of the p arm).

Duplication

- Direct: a segment of chromosome is repeated, once or several times, the duplicated segment keeping the same orientation with respect to the centromere.
- Inverted: the duplicated segment takes the opposite direction.
- Recorded as $\text{dup}$, followed by a bracket with the # of the chromosome, and a second bracket indicating the breakpoint(s) and the duplicated region.
Examples

- **46,XX,del(14)(q23)=**
  Female with 46 chromosomes with a deletion of chromosome 14 on the long arm (q) at band 23.

- **46,XY,dup(14)(q22,q25)=**
  Male with 46 chromosomes with a duplication of chromosome 14 on the long arm (q) involving bands 22 to 25.

- **47,XY,+21=**
  Male with 47 instead of 46 chromosomes and the extra is a 21.

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### Main chromosome anomalies in malignant blood diseases

<table>
<thead>
<tr>
<th>#</th>
<th>Chromosome anomaly</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chrom. 1 rearrangements</td>
<td>Various</td>
</tr>
<tr>
<td>2</td>
<td>t(2;8)(p23;q11)</td>
<td>L3-ALL and Burkitt</td>
</tr>
<tr>
<td>3</td>
<td>t(4;11)(q21;p15)</td>
<td>ALL</td>
</tr>
<tr>
<td>4</td>
<td>del(5q) or -5</td>
<td>MDS, ANLL, 2nd Leuk.</td>
</tr>
<tr>
<td>5</td>
<td>del(6q)</td>
<td>CLL</td>
</tr>
<tr>
<td>6</td>
<td>del(7q) or -7</td>
<td>MDS, ANLL, 2nd Leuk.</td>
</tr>
<tr>
<td>7</td>
<td>t(8;14)(q24;q32)</td>
<td>See chromosome 2</td>
</tr>
<tr>
<td>8</td>
<td>t(8;14)(q24;q11)</td>
<td>L3-ALL and Burkitt</td>
</tr>
<tr>
<td>9</td>
<td>t(8;14)(q11;q32)</td>
<td>T-ALL</td>
</tr>
<tr>
<td>10</td>
<td>t(9;22)(q34;q11)</td>
<td>M2-ANLL</td>
</tr>
<tr>
<td>11</td>
<td>t(9;22)(q34;q11)</td>
<td>Various, myeloid</td>
</tr>
<tr>
<td>12</td>
<td>t(9;22)(q21;q11)</td>
<td>CML, ANLL, ALL, various</td>
</tr>
<tr>
<td>13</td>
<td>t(11;14)(p13;q32)</td>
<td>See chromosome 4</td>
</tr>
<tr>
<td>14</td>
<td>t(11;14)(q13;q32)</td>
<td>T-ALL</td>
</tr>
<tr>
<td>15</td>
<td>del(11q)</td>
<td>ANLL, CLL</td>
</tr>
<tr>
<td>16</td>
<td>+12</td>
<td>CLL, NHL</td>
</tr>
<tr>
<td>17</td>
<td>t(12;21)(p13;q22)</td>
<td>ALL</td>
</tr>
<tr>
<td>18</td>
<td>del(13q)</td>
<td>Various</td>
</tr>
<tr>
<td>19</td>
<td>t(14;18)</td>
<td>See chromosome 8</td>
</tr>
<tr>
<td>20</td>
<td>t(15;17)(q22;q11)</td>
<td>See chromosome 11</td>
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<tr>
<td>21</td>
<td>t(15;17)(q22;q11)</td>
<td>M5-ANLL</td>
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<tr>
<td>22</td>
<td>16q22 rearrangement</td>
<td>See chromosome 15</td>
</tr>
<tr>
<td>23</td>
<td>inv(16)(p13q22)</td>
<td>T-lymphocyte</td>
</tr>
<tr>
<td>24</td>
<td>t(15;17)(p11;q22)</td>
<td>See chromosome 15</td>
</tr>
<tr>
<td>25</td>
<td>i(15;17)(p11;q22)</td>
<td>T-ALL</td>
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<tr>
<td>26</td>
<td>t(15;17)(q22;q11)</td>
<td>See chromosome 15</td>
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<tr>
<td>27</td>
<td>del(20q)</td>
<td>myeloid</td>
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<tr>
<td>28</td>
<td>t(8;21)(q22;q22)</td>
<td>See chromosome 8</td>
</tr>
<tr>
<td>29</td>
<td>t(12;21)(q13;q22)</td>
<td>See chromosome 12</td>
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<tr>
<td>30</td>
<td>t(9;22)</td>
<td>See chromosome 9</td>
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<tr>
<td>31</td>
<td>del(19q)</td>
<td>Hyperplasy</td>
</tr>
<tr>
<td>32</td>
<td>t(14;18)(q32;q21)</td>
<td>Hyperplasy</td>
</tr>
</tbody>
</table>

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**Other hypoploidy**

2nd Leuk., ALL, NHL
Helpful Web Sites

- http://atlasgeneticsoncology.org
- http://www.chromodisorder.org

If in doubt ask

- Cytogenetics lab
- Hematologist / Oncologist
- DIANE!