Medical Genetics & Cancer

I. Genetic disorders
A. Does a disease have a genetic basis?
B. Using pedigrees to determine inheritance patterns

II. Genetic disorders & the immune system
A. X-linked agammaglobulinemia (XLA)
B. Severe combined immunodeficiency (SCID)
C. X-linked Hyper IgM Syndrome

III. Oncogenes & Cancer
A. Normal v. Malignant
B. transformation of proto-oncogenes
C. tumor-suppressor genes
D. Viral caused cancers

A. Determining whether or not a disease has a genetic basis:
1) When an individual exhibits a disease, the disorder is more likely to occur in genetic relatives than in the general population
2) Identical twins share the disease more often than non-identical twins
3) The disease does not spread to individuals sharing similar environmental situations
4) Different populations tend to have different frequencies of the disease
5) The disease tends to develop at a characteristic age (age of onset)
6) The human disorder may resemble a disorder that is already known to have a genetic basis in an animal.
7) A correlation is observed between a disease and a mutant human gene or a chromosomal disorder.

I. Genetic disorders
• most likely a significant underestimate
• One of the most difficult problems facing scientists is to learn how genes contribute to disease that have a complex pattern of inheritance involving several genes!

Characterized genetic disorders
• Albinism
• Atraxia telangiectasia
• Bloom syndrome
• Cystic fibrosis
• Fanconi anemia
• Galactosemia
• Phenylketonuria
• Sickle cell anemia
• Thalassemia
• Xeroderma pigmentosum
• Tay-sachs disease
• Muscular dystrophy
• Achondroplasia
• Brachydactyly
• Camptodactyly
• Crouzon syndrome
• Ehlers-Danlos syndrome
• Familial hypercholesterolemia
• Adult polycystic kidney disease
• Huntington disease
• Hypercalcemia
• Marfan syndrome
• Nail-patella syndrome
• Porphyria
B. Using pedigrees to determine inheritance patterns of disease

- When a disorder is caused by a mutation in a single gene, the inheritance pattern can be deduced by analyzing pedigrees, and data can be pooled from many large pedigrees.
- When we do not know the actual genetic defect underlying the disease or if great number of diverse mutations in the disease gene exist, one can still consult families in risk, provided we know the approximate chromosomal localization of the causal genetic defect.
- We can simply use a genetic marker occurring at that place of the genome, type the healthy as well as afflicted persons in the family and try to deduce, which allele of the polymorphism is linked to the disease allele and predict thus the genotype in the disease locus and evaluate the risk in prenatal or pre-symptomatic or to identify carriers.
- Disadvantage of the indirect method is the need of complete family, with already afflicted members.
- Another complication is that in each family, the disease will be in general linked to a different allele of the polymorphism (it is only linkage, not cause of the disease). Some families will be thus uninformative for a given polymorphism and we will have to be screened for more polymorphic loci till we find an informative one.

Lod score

- “Log of odds” – method to obtain a more reliable linkage estimate from single matings
  - the most commonly used statistic, based on the direct comparison of probability of null hypothesis, stating that there is no linkage (recombination fraction 1/2), with the alternative hypothesis, claiming there is linkage with a certain recombination fraction \( \theta \).
  - Measures the log10 of the likelihood that a particular set of linkage data would be obtained if two genes are linked, divided by the likelihood that the same data would be obtained if the genes were unlinked.
  - Assess the probability that a pedigree involving 2 traits reflects linkage.

Using Lod scores

- Evaluate the pedigrees for the trait for two hypotheses (1) that the loci are linked and a specific distance apart and (2) the loci are not linked.
- Compare the two results in a particular way, and get the likelihood that the first hypothesis is right.
- If Lod is greater than 0, data are consistent with linkage, negative lod scores indicate independent assortment.
- Lod scores of 3.0 or higher cause general acceptance of linkage model; this value means that linkage (at the particular distance tested) is 1,000 times more likely than independent assortment.

<table>
<thead>
<tr>
<th>RF</th>
<th>0.5</th>
<th>0.4</th>
<th>0.3</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.25</td>
<td>0.3</td>
<td>0.35</td>
<td>0.4</td>
</tr>
<tr>
<td>R</td>
<td>0.25</td>
<td>0.2</td>
<td>0.15</td>
<td>0.1</td>
</tr>
</tbody>
</table>

For an RF of 0.2, the probability is:
0.4 x 0.1 x 0.4 x 0.4 x 0.4 x B
=0.00256 x B

The ratio of the two = 2.62, hence the hypothesis of RF 0.2 is 2.62x’s more likely; the Lod score is 0.4
II. Genetic disorders & the immune system
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II. Oncogenes & Cancer
Cancer =
Oncogene =

Oncoprotein =

1. Transformation – conversion of a normal cell into a malignant cell (neoplastic).
2. Immortalization
3. Metastasis
A. Normal v. Malignant cells

Normal Cell culture features:
1) Anchorage dependence
2) Serum dependence
3) Density – dependent inhibition
4) Cytoskeletal organization

1. transformation

- Immortalization and aneuploidy: survival and continuous growth beyond normal limits involves changes at the telomere that frequently result in major chromosomal rearrangements.
- Partial or complete loss of growth factor dependence:
- Loss of contact inhibition:
- Loss of anchorage requirement:
2. Cancer is a gene disorder
   * Usually multiple genetic changes needed to create cancer
   * Carcinogens – mutagens that increase the frequency of cell transformation

B. transformation of proto-oncogenes
   * proto-oncogenes: normal genes found in an animal's genome
     – Proto-oncogenes code for cellular proteins that relay signals, stimulating growth; these cellular proteins are responding to signals from other cells.
Alterations of proto-oncogenes:
1) proto-oncogene can insert itself into new places in genome
2) can be amplified, increasing the # of copies of the gene

Results of altered proto-oncogenes “stuck accelerator”
- overproduction of growth factors;
- flooding of the cell with replication signals;
- protein kinases (enzymes that add phosphate groups to target proteins);
- uncontrolled stimulation in the intermediary pathways; and/or
- unrestrained cell growth driven by elevated levels of transcription factors.

Example: ras genes
- Ras protein forms a complex that is triggers signaling system which activates cell proliferation. Responds to growth factors
- Mutation of ras causes over-activity
- ras wild type: GGC GCC GGC GGT GTG GGC
- Mutant: GGC GCC G TC GGT GTG GGC
  - Results in Val instead of Gly, the Ras oncoprotein can’t hydrolyze GTP to GDP, so it remains in the active Ras-GTP state!

C. tumor-suppressor genes
- Trigger apoptosis
  - e.g. BRCA1, NF1, p16, p53, WT1, RB
  - i.e. p53 Prevents transcription of genes required for passage through G1 checkpoint
- Uncontrolled growth is not suppressed because inhibitory activity is lost when these genes are altered
Knudson’s 2 hit hypothesis

- Example: Retinoblastoma
- Two genetic events affect the two normal copies of the tumor suppressor gene RB1

First hit: an RB1 mutation (RBx) on chromosome 13q14 results in a heterozygous retinoblast. During mitosis, a non-disjunction event occurs, resulting in a daughter cell with only a single copy of chromosome 13 containing RBx. (d) Chromosome 13 reduplicates, resulting in a cell homozygous for the RBx mutation. After this ‘second hit’ the cell has lost RB protein function and has malignant potential.

D. Tumor viruses

- ~15% of cancers are caused by viruses
- Virus throws a regulatory switch that changes the growth properties of the cell
- Oncogenic retroviruses, have an oncogene that gives them the ability to transform the host

<table>
<thead>
<tr>
<th>Viral class</th>
<th>Type of virus</th>
<th>Genome size</th>
<th>Oncocenes</th>
<th>Origin of onccogene</th>
<th>Action of oncogene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyoma</td>
<td>dsDNA</td>
<td>5-6 kb</td>
<td>T antigens</td>
<td>Early viral gene</td>
<td>Initiates tumor suppressor</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>dsDNA</td>
<td>~0.6 kb</td>
<td>E1 and E2</td>
<td>Early viral gene</td>
<td>Initiates tumor suppressor</td>
</tr>
<tr>
<td>Retrovirus (acute)</td>
<td>ssRNA</td>
<td>6-9 kb</td>
<td>Individual</td>
<td>Early viral gene Cellular</td>
<td>Activates oncogenic pathway</td>
</tr>
</tbody>
</table>

Tumor-virus pathway:

1. Virus infects host cell.
2. Viral DNA is integrated (randomly) in host chromosome.
3. Viral genes are transcribed and translated constitutively.
4. Viral oncogene products (oncoproteins) interfere with normal controls on cell growth and proliferation.
Multi-step model for colon cancer:
1. loss of tumor-suppressor gene APC (polyp develops)
2. activation of ras
3. loss of tumor suppressor gene DCC (tumor malignant)
4. loss of tumor suppressor gene p53
5. Additional mutations & then metastasis