Polygenic and multifactorial inheritance/disorders

HGD5502 – Medical Genetics
1st November, 2011

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Source: http://wiringthebrain.blogspot.com/
<table>
<thead>
<tr>
<th><strong>Terminology</strong></th>
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<tbody>
<tr>
<td><strong>Trait</strong></td>
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<tr>
<td><strong>Single gene trait</strong></td>
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<tr>
<td><strong>Polygenic trait</strong></td>
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<tr>
<td><strong>Multifactorial trait</strong></td>
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<tr>
<td><strong>Pure polygenic trait</strong></td>
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<tr>
<td><strong>Quantitative trait</strong></td>
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<td><strong>Qualitative trait</strong></td>
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</tbody>
</table>
Heritability estimates the genetic contribution to the variability of a trait.
Anatomy of trait – example of polygenic disorders

Penetrance – percent of individuals with a genotype who have the associated phenotype.

Frequency – how common they are.

Source: nature.com
Examples of heritable multifactorial polygenic traits

Source: babble.com

Source: psychologytoday.com

Source: sbc.ubc.ca

Source: fatburnweightloss.com
Examples of Multifactorial Polygenic Traits (Non-Mendelian Genetic Inheritance)

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Discontinuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>Cleft lip &amp; palate</td>
</tr>
<tr>
<td>Hair colour</td>
<td>Skin colour</td>
</tr>
<tr>
<td>Obesity</td>
<td>Obesity</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Congenital Heart disease</td>
<td>Congenital Heart disease</td>
</tr>
<tr>
<td>Fingerprint</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Pyloric stenosis</td>
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</table>

Phenotypes vary over a continuous range of measurement

Quantitative traits

Only a few distinct phenotypes

Discrete traits
Polygenic inheritance and the normal distribution

Inheritance of a polygenic trait involves many genes:

- At different loci
- Each gene exerts a small additive/cumulative effect
- No one gene is dominant or recessive to another
- Also known as *quantitative* inheritance

Resembles normal continuous distribution

The normal (Gaussian) distribution
Genes for ‘Tall-ness’

**Scenario I**
- 2 alleles
- Equal frequency
- At a single locus
- E.g. A=tall, B=short

### Single locus

**OUTCOMES**
- 1 Tall (AA) :
- 2 Average (AB/BA) :
- 1 Short (BB)
Genes for ‘Tall-ness’

**Scenario II**
- 2 alleles
- Equal frequency
- At a 2 separate loci
- E.g. A=tall, B=short

**OUTCOMES**
1 Very Tall (AAAA) :
4 Tall (AAAB) :
6 Average (AABB) :
4 Short (ABBB) :
1 Very Short (BBBB)
Genes for ‘Tall-ness’

**Scenario III**

- 2 alleles
- Equal frequency
- At a 3 separate loci
- E.g. A=tall, B=short

<table>
<thead>
<tr>
<th>Locus 1</th>
<th>Locus 2</th>
<th>Locus 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>BA</td>
<td>BA</td>
<td>BA</td>
</tr>
<tr>
<td>BB</td>
<td>BB</td>
<td>BB</td>
</tr>
</tbody>
</table>

**OUTCOMES**

1 Extreme Tall : 6 Very Tall : 15 Tall : 20 Average : 15 Short : 6 Very Short : 1 Extreme Short
Genes for ‘Tall-ness’

When number of loci involved in the Tall trait = N

• 2 alleles
• Equal frequency
• At a ‘N’ separate loci
• E.g. A=tall, B=short

Values for each genotype = Binomial expansion \((A+B)^{2N}\)

Where,

\[ A=B=\frac{1}{2} \text{ (equal frequency)} \]
\[ N=\text{number of loci involved} \]

E.g. When \(n=1\) (single locus)

\[(A+B)^{2N} = (A+B)^{2(1)}\]
\[= (A+B) \times (A+B)\]
\[= A^2 + AB + AB + B^2\]
\[= A^2 + 2AB + B^2\]
Therefore, ‘Tall-ness’ trait is a quantitative trait with continuous normal distribution

Year 1920
– 175 cadets at Connecticut Agricultural College lined up by height

Year 1997
– students the same school (now Uni. Of Connecticut) lined up by height
Total ridge counts between landmark points A and B on all fingers
Polygenic inheritance – Skin colour

Variation in skin colours based on a model of three genes and two alleles each.
Liability:
• All factors that influence the development of a multifactorial disorder.
• Can be genetic or environmental factors.
• Cannot be measured but can be determined from the incidence of the disease in a group using statistics of the normal distribution.
• The units of measurement are SD – can be used to estimate correlation between relatives.
• E.g. several ‘bad’ genes and adverse environmental factors
Familial correlation for quantitative traits

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Proportion of genes shared</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First degree</strong></td>
<td>½ (50%)</td>
</tr>
<tr>
<td>Between you and:</td>
<td></td>
</tr>
<tr>
<td>1. Parents</td>
<td></td>
</tr>
<tr>
<td>2. Siblings</td>
<td></td>
</tr>
<tr>
<td>3. Children</td>
<td></td>
</tr>
</tbody>
</table>

| **Second degree**   | ¼ (25%)                    |
| Between you and:    |                            |
| 1. Uncles and aunts |                            |
| 2. Nephews and nieces |                         |
| 3. Grandparents     |                            |
| 4. Grandchildren    |                            |
| 5. Half-siblings    |                            |

| **Third degree**    | 1/8 (12.5%)                |
| Between you and:    |                            |
| 1. First cousins    |                            |
| 2. Great-grandparents |                      |
| 3. Great-grandchildren |                        |

*Correlation* is a statistical measure of the degree of association of variable phenomena OR known as degree of resemblance or relationship between two parameters.
**Heritability**

- proportion of the total phenotypic variance of a condition that is caused by additive genetic variance in a certain population at a certain time
- the greater the value for the heritability the greater the role of genetic factors
- $H$ value = 1 => a trait whose variability is completely the result of gene action
- $H$ value = 0.2 => phenotypic variation is 20% due to *genetic variation*
Gene hunting strategies

Strategy to find disease susceptibility genes for type 2 diabetes mellitus
**Gene hunting – Linkage analysis**

**Linkage analysis**
Mapping of single-gene disorders by studying the co-segregation of genetic markers with disease

**Disadvantages of linkage analysis**
- difficult to develop strategies for detecting linkage of additive ‘polygene’
- Variable age of onset – genetics status of unaffected family members cannot be known with certainty
- Heterogeneous etiology – coronary artery disease and schizophrenia

**Improvement of linkage analysis**
- Sample an ‘ideal’ population
- a LARGE population – genetically homogenous
- Few thousands participants / samples

*Sibling-pair analysis*
Gene hunting – Association studies

**Association studies**

- Involved cases and matched controls
- To see whether two alleles or phenotypes occur together in a population in a non-random manner with *statistical significance*
- Alleles that confer only weak susceptibility to a complex disease may be more easily found through this study than linkage studies

**Challenges of association studies**

- Association of an allele with a phenotype does not prove that one causes the other
- Difficult to reproduce similar observations in different populations or by other investigators
- Required further confirmation in larger samples consisting of more heterogeneous multi-ethnic population
Gene hunting – Association Studies

People with disorder

Patient DNA

Disease-specific SNPs

Compare differences to discover SNPs associated with disease

People without disorder

Non-Patient DNA

Nondisease SNPs
Gene hunting – Association Studies

Initial study
800 cases/800 controls
~ 500,000 Tag SNPs

Follow-up study #1
2,000 cases/2,000 controls
~ 25,000 SNPs

Follow-up study #2
2,000 cases/2,000 controls
> 1,500 SNPs

Gene identification
~ 25 specific genes
## Gene hunting – Twin studies

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic / identical twins</th>
<th>Dizygotic / fraternal twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles common at every locus</td>
<td>No more alike genetically than any two siblings – 50% shared genes</td>
<td></td>
</tr>
<tr>
<td>Similar early embryonic/fetal development – sharing the same placenta but rarely the amniotic sac</td>
<td>Different early embryonic/fetal development – different placenta and different amniotic sac</td>
<td></td>
</tr>
</tbody>
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Natural subjects to study the influence of environment on a trait

**Concordance**

**Disconcordance**

Reunited twins for testing ‘nature or nurture’
Which of the disorder is highly to be genetically determined?
The disease:
- Multifactorial congenital disorder
- A type of discrete trait
- Caused by abnormal closure of the embryonic neural tube in week 3 or 4 of gestation

The genetic:
- Involved more than 80 genes

The environment:
- Women who gave birth to infants with NTDs had high homocysteine levels in their blood

The risk:
- 3-4% recurrence risk in siblings
MTHFR MISSENSE MUTATION AT BASE PAIR 677 (ALANINE TO VALINE)

THERMOLABILE 5,10-METHYLENE TETRAHYDROFOLATE REDUCTASE

5, 10-METHYLENETETRAHYDROFOLATE

5-METHYLTETRAHYDROFOLATE (MAJOR CIRCULATING FOLATE FORM)

METHIONINE

ADOMET

THF

VITAMIN B12

HOMOCYSTEINE

MTHFR MISSENSE MUTATION AT BASE PAIR 677 (ALANINE TO VALINE)
HYPERHOMOCYSTEINEMIA

(> 15 µmol/L) WHO, 1994
HYPERHOMOCYSTEINEMIA

MTHFR VARIANTS

DECREASED FOLIC ACID

VITAMIN B12 DEFICIENCY

AGE
SEX
BMI
CIGARETTE SMOKING
COFFEE CONSUMPTION
DIET

NTD – Homocysteine metabolism
Metabolic disorders – Type II Diabetes Mellitus

Source: savvyhealthfitness.com
The disease:
• Multifactorial adult onset polygenic disorder
• A type of quantitative trait
• A chronic and extremely heterogeneous disorder with NO cure
• See previous slide for the cause of the disorder

The genetic:
• Glucokinase (GSK), hepatocyte nuclear factor 4-alpha (HNF4A) and peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and many more

The environment:
• What can I say more? Anything that cause high blood pressure, high blood triglycerides level, gestational diabetes, giving birth to a baby >9 pounds, high fat/alcohol intake, sedentary lifestyles, obesity/overweight, aging

The stats:
• 8% of adults in USA have T2DM
• 1.2 million Malaysian have T2DM
• Moderate exercise resulting in 5-7% weight loss reduced the likelihood of disease by 60-70%
Neurological disorder – Alzheimer’s disease

• 60-70% – progressive cognitive impairment among elderly
• Progressive dementia & memory loss
• Formation of amyloid plaque & neurofibrillary tangles
• 10% autosomal dominant but mostly multifactorial
• ↑ risk – with affected first degree relative
• Genetic-mutation in 3 genes
  • presenilin (PS1 & PS2) – cleavage amyloid-β precursor protein (APP)
    → mutation causes APP not cleaved normally → deposition of amyloid
  • APP mutation – disrupt normal cleavage of APP by presenilin
  • Apolipoprotein E (APOE) – involves in clearance of amyloid from brain
Cancers

The disease:
• Multifactorial polygenic disorder
• Leading cause of death

The genetic:
• Various genes
  • BRCA1 and BRCA2 genes for breast cancer
  • APC, AXIN2, TP53, STK11, PTEN etc for colon cancer

The environment:
• Tobacco – Lung cancer
• Infectious agents
  • HPV – cervical cancer
  • Hepatitis B & C viruses – hepatocarcinoma
  • EBV – nasopharyngeal cancer
• Diet
Medical Genetics for the Modern Clinician  
*by Judith Westman (Lippincott Williams & Wilkins), Year 2006.*

Human Genetics: concepts and applications  
*by Ricki Lewis (McGRAW-HILL), Year 2010.*

EMERY’s Elements of Medical Genetics  
*by Peter Turpenny and Sian Ellard (Churchill Livingstone), Year 2010.*
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