Quantitative genetics: traits controlled by alleles at many loci

Human phenotypic adaptations and diseases commonly involve the effects of many genes, each with small effect.

Quantitative genetics allows analysis of selection and genetic bases of quantitative phenotypic traits, such as height, weight, blood pressure, IQ, liability to schizophrenia, all other polygenic diseases.

What phenotypic traits have evolved in human lineage? What is their genetic basis?

Some of the big questions of quantitative genetics analysis

• How do genetics and the environment affect a trait?
• Which and how many genes produce a set of phenotypes for a trait; where in the genome are they located?
• Do some genes play a major role, whereas other genes modify or play a small role?
• How does selection affect the trait? What form of selection?

Some quantitative phenotypic traits that evolved along the human lineage, or in some populations

1. Large brain size
2. Light skin color
3. Africanaity at birth
4. Longer juvenile period
5. Smaller teeth
6. Relative hairlessness
7. Increased susceptibility to cancer, heart disease
8. Language skills, technical skills

Quiz on population vs. quantitative genetics

Population vs. quantitative genetics

<table>
<thead>
<tr>
<th>Mendelian traits: discrete variation</th>
<th>Quantitative traits: continuous variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td>Number of individuals</td>
</tr>
<tr>
<td>Trait value</td>
<td>Trait value</td>
</tr>
<tr>
<td>Number of individuals</td>
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</tr>
<tr>
<td>Trait value</td>
<td>Trait value</td>
</tr>
</tbody>
</table>

Alleles and genotypes | Means and variances

Types of quantitative traits

Quantitative traits may be:
• Continuous trait
• Meristic trait
• Threshold trait

Distribution (frequencies)

Continuum between population and quantitative genetics

<table>
<thead>
<tr>
<th>One gene</th>
<th>Two genes</th>
<th>Four genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa</td>
<td>A, A</td>
<td>A, A, A, A</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Phenotypic variation: size or weight
Variation in quantitative traits arises from the combined effects of:
- Genes at multiple loci
- Pleiotropy (one gene having many effects)
- Epistasis (different genes interacting)
- Environmental effects (genes produce a range of phenotypes, depending upon the environment - phenotypic plasticity and reaction norms)

Population genetics

Quantitative genetics

S, the selection differential

R, the selection response,

To predict change in trait: $R = h^2 S$
For Mendelian traits we analyze alleles/genotypes; For quantitative traits we analyze variation (variance)

**Main variance components**

\[ V_P = \text{total phenotypic variance} \]
\[ V_P = V_A + V_E + V_{GXE} \]

- \( V_A \): Additive genetic variance
- \( V_E \): Variance among individuals experiencing different environments
- \( V_{GXE} \): Variance due to environmental variation that influences gene expression

**Heritability**

\[ h^2 = \frac{V_A}{V_P} \]

The proportion of phenotypic variance due to additive genetic variance among individuals

\[ h^2 = \frac{V_A}{V_A + V_E + V_{GXE}} = \frac{V_A}{V_{\text{total}}} \]

Heritability can be low due to: low genetic variability, highly variable environment, other factors raising \( V_{\text{total}} \) or lowering \( V_A \)

Heritability is always population-specific and it does not imply ‘genetic determinism’ in any way

A mean difference between populations, and high heritability, does not imply genetic ‘determinism’: EXAMPLES, ability to do math in school, myopia

**Estimating heritability, \( h^2 \)**

1. Analyze related individuals: twins of different type, or parents and offspring
2. Measure the response of a population, in the next generation, to selection

**Measuring heritability from analysis of DZ and MZ twins**

Dizygotic (DZ) twins: two egg twins, same degree of genetic relatedness as normal siblings (50% of genes in common)

Monozygotic (MZ) twins: one egg twins genetically identical (100% of genes in common)

**CORRELATION**

Twin 1

Twin 2

DIZYGOTIC TWINS

**CORRELATION**

Twin 1

Twin 2

MONOZYGOTIC TWINS
\[ h^2 = 2(r(MZ) - r(DZ)) \]

Where \( r \) stands for the correlation between twins

Measuring \( h^2 \): Parent-offspring regression

Heritability of different human traits

<table>
<thead>
<tr>
<th>TRAIT</th>
<th>HERITABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingerprint pattern</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Height</td>
<td>0.7</td>
</tr>
<tr>
<td>IQ</td>
<td>0.7</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.7</td>
</tr>
<tr>
<td>Autism, schizophrenia</td>
<td>0.3-0.6</td>
</tr>
<tr>
<td>Weight</td>
<td>0.5</td>
</tr>
<tr>
<td>Cholesterol level</td>
<td>0.45</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.4</td>
</tr>
<tr>
<td>Handedness</td>
<td>0.3</td>
</tr>
<tr>
<td>Fertility</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Three modes of phenotypic selection:

- Directional selection
- Stabilizing selection
- Disruptive selection

Distribution of birth weight among 13,730 children in England
Stabilizing selection, and optimization, for human birth weight
Bigger (heavier) is better, to a point
Ancestral environments?

Unifying population and quantitative genetics: QTLs and genes of major and minor effects

How important are alleles of major and minor effect in adaptation and disease?
What ARE the genes/alleles underlying adaptation and disease and what do they do?

Basic genetic model

100s, 1000s of common, small effect, risk alleles

De novo 'liability' + Inherited polygenic 'liability' = Total genetic liability

Basic genetic model

Deviation from mean due to common alleles inherited from parents

How connect quantitative traits with actual genes, to find genes 'for' traits?

QTLs = Specific genomic regions correlated with continuous phenotypic trait variation

Identify QTLs by identifying co-inheritance of specific genetic marker alleles (such as Single Nucleotide Polymorphism or microsatellites) with the phenotypic trait
**FINDING THE GENES underlying human health and disease, for quantitative traits**

1. **Full genome scans** -> regions with genes associated with the phenotype (GWAS)
2. **Fine-scale scans of promising regions**
3. **Identify candidate genes** based on their position and function
4. **Conduct association studies** -> for specific gene, do allele frequencies vary between individuals that vary in the phenotype?
5. **Seek to replicate in different populations**
6. **Conduct studies of function, expression in humans**
7. **Create mouse ‘knock-outs’ or ‘knock-ins’**

Might also (8) **Test for positive selection** on gene in human lineage; compare evolution of gene in different species

**Table 5.1**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Gene</th>
<th>Chromosome location</th>
<th>Clinical variant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>A0M09</td>
<td>2q13</td>
<td>-15707198 C&gt;T</td>
<td>Ballew et al. (2007)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>APOE</td>
<td>19q13</td>
<td>-1990939 C&gt;T</td>
<td>Soler et al. (2005)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>ABCB1</td>
<td>17q21</td>
<td>-15282000 C&gt;T</td>
<td>Details et al. (2006)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>MCLD5</td>
<td>4q31</td>
<td>-14060219 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Cholesterol concentration</td>
<td>MTHFD1</td>
<td>7q31</td>
<td>-19999999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>LPL</td>
<td>19q13</td>
<td>-15299999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>APOB</td>
<td>19q13</td>
<td>-15299999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>PNPLA3</td>
<td>1q21</td>
<td>-17999999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>CYP3A5</td>
<td>21q22</td>
<td>-19999999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>CYP7A1</td>
<td>21q22</td>
<td>-19999999 C&gt;T</td>
<td>Reddel et al. (2006)</td>
</tr>
</tbody>
</table>
Gene ‘for’ a trait means what, exactly?

Allelic variation in the gene is associated with variation in the trait, to some degree, in one or more populations, at one or more times.

Gene does not ‘cause’ the trait - could always change the environment, and gene may no longer be a gene ‘for’ this trait.

BRCA1 - gene ‘for’ breast cancer? No, gene that mediates DNA repair/proliferation tradeoff, also notably expressed in brain, has undergone selection.

Example: Schizophrenia and handedness

-Schizophrenia underlain by many genes of small to moderate effect, heritability is high, is associated with mixed/right handedness
-Is a disorder of language and cognition, may, in part, be by-product of very strong recent selection for language and social cognition
-May exhibit a ‘cliff-edged fitness function’

Parent-of-origin effects on handedness and schizophrenia susceptibility on chromosome 2p12–q11

Clyde Frangula1, Lynne E. DeLanoy1, Sarah H. Shaw1, Simon E. Fisher1, Alex J. Richardson1, John F. Semin2 and Anthony P. Monaco2

2003

Evidence for positive selection of LRRTM1 gene in human population, from human HAPMAP data

What’s up with LRRTM1?! Work in progress...

The present and future of genomics, and health

1 ‘Chips’ can genotype >100,000 SNPs at once
2 Whole-genome sequencing or salient-SNP genotyping will soon cost 1000s of $ or less per individual -> dawn of ‘personalized medicine’
3 Individuals (or in vitro embryos or tumors) can be genotyped for a tremendous range of alleles involved in drug metabolism (pharmacogenomics), disease risk, and genetic effects on nutrition (nutrigenomics)
4 Evolutionary histories and bases of disease risk alleles can be analyzed much more readily
Relation of genetics to ultimate causes of variation in health and disease

(a) Novel environments
(b) Novel genes, genotypes (via mutation, drift, inbreeding, gene flow, selection)
(c) Tradeoffs between opposing selective pressures
(d) Conflicts within and between species
(e) Constraints on optimization (evolutionary legacies)
(f) Trait involves benefits to own reproduction, or to kin, that offset costs to phenotype (genes that increase reproduction spread even if they decrease health, happiness or longevity)
(g) Trait is not a disease but a beneficial protective response (eg cough, fever, pain, nausea, vomiting, anxiety, fatigue)

GENETIC BASIS OF DISEASES

Box 1  Why humans continue to evolve despite the many benefits of hygiene and modern medicine

Within the context of the publication of ‘The Origin of Species’, the misconception developed that modern hygiene and medical care have caused natural selection to stop working on human populations. This view failed by another misconception that selection operates only through differences in survival. We now know that natural selection on traits occurs whenever there is variation among individuals in fitness and in traits when the variation in traits is correlated with the variation in fitness. A response to selection will then follow part of the variation in the traits in heritable. A great story for fitness is lifetime reproductive success (LRS) or number of children per parent lifetime. LRS has both a survival component — e.g. mortality and reproductive age — and a reproductive component. Great hygiene and medical care that reduces prenatal, infant and child mortality reduce the variation among individuals in the survival component. However, they do not eliminate natural selection, as substantial variation remains in individuals in the reproductive component measures. For example, consider an extreme case in which medical and public health measures were so good that everyone was born around age 50. This would not affect natural selection, as individuals would still differ in their LRS and that variation would drive natural selection. The potential for natural selection only varies when all individuals had exactly the same reproductive success or when traits is correlated with the variation in reproductive success that still exists. These states are unlikely ever to occur in any population. The effect of culture on biology varies interestingly. Birth control, assisted reproductive technology and the like operated so effect that they could not exist today. The selective pressures that have driven the evolution of modern human societies cannot deal with it regarding them as part of a changing environment that is changing selection intensities. A more fundamental solution awaits the development of methods of analyzing gene-environment evolution that can be applied to large, longitudinal human data sets.

It’s not just finches...

Measuring selection in contemporary human populations

Stephen C. Stearns**, Sean C. Byars**, Distinguished R. Covindaraju** and Daughts Eiko**

Abstract. Like humans, other species? This question can be answered using data on lifetime reproductive success, multiple traits and genetic variation and covariation in these traits. Such data are available: mating-long term, multigeneration studies — both clinical and epidemiological — but they have not been widely used to address contemporary human evolution. Here we review methods to predict evolutionary change and attempts to measure selection and inheritance in humans. We also assemble examples of long-term studies in which additional measurements of evolution could be made. The evidence strongly suggests that we are evolving and that our nature is dynamic, not static.

Detect ancestral/derived haplotypes; for what traits do they differ?

‘Phenomics’

Combine with heritability, predict responses to selection, effects on health...