Basics of Heredity

João Paulo Oliveira

Basic Genetics for ART Practitioners
ESHRE Campus 2010
Porto, Portugal, 16 April 2010
Organised by the ESHRE Special Interest Group "Reproductive Genetics"

Heredity and Genetics

- ***Heredity***:
  the transmission of characteristics of parents to offspring.

  The Living Webster Encyclopedic Dictionary of the English Language.
  The English Language Institute of America, Inc., 1972.

- ***Genetics***:
  the scientific study of the principles of heredity and the variation of inherited traits among related organisms.

  The American Heritage® Science Dictionary.
  Houghton Mifflin Company, 2005.

Unity and Diversity

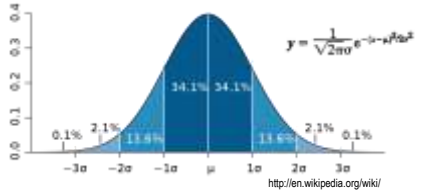
- Biological systems show remarkable unity at the molecular and cellular levels, reflecting their common ancestry.
- Variations on this unity lead to the extraordinary diversity of individual organisms.

The scientific analysis of heredity deals with the explanation of two major paradigms of life:
- the **unity** of species
- the **diversity** of individuals.

Classes of Phenotypes and Historical Aspects

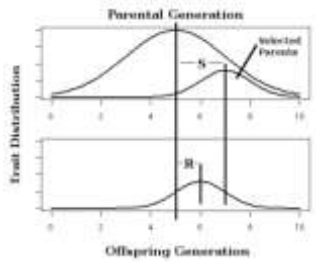
Quantitative Variation

Most of the normal phenotypic variation among individuals is quantitative, continuous and normally distributed in populations.



http://en.wikipedia.org/wiki/

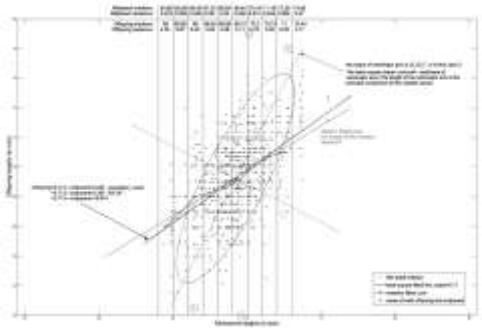
Response to Selection



Continuous, heritable traits respond to selection in a predictable fashion.

$R = h^2 * S$
(h^2 : narrow sense heritability)

[http://en.wikipedia.org/wiki/]



Modified from http://en.wikipedia.org/wiki/File:Galton_experiment.png

Galton's Ancestral Law of Heredity

"...the total heritage of the offspring is derived as follows.
The two parents between them, contribute on the average one half of each inherited faculty, each of them contributing one quarter of it. The four grandparents contribute between them one quarter, or each of them one sixteenth; and so on, the sum of the series 1/2 + 1/4 + 1/8 + 1/16 + &c. being equal to 1..."

Francis Galton. A diagram of heredity. Nature 1898;57:293.

Dimorphic Features of Garden Peas

Plant structure	trait	phenotype	
ripe seeds	surface	*round*	*wrinkled*
seed interiors	colour	*yellow*	*green*
petals	colour	*purple*	*white*
unripe pods	colour	*green*	*yellow*
ripe pods	colour	*inflated*	*pinched*
flowers	position	*axial*	*terminal*
stems	length	*long*	*short*

Mendel's experiments data

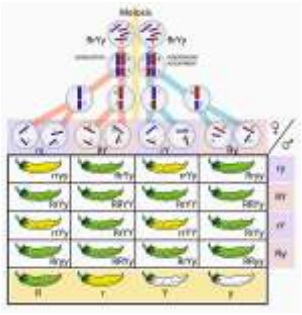
Parental phenotype	F_1	F_2	F_2 ratio
Round x *wrinkled* seeds	all *Round*	5474 *Round* : 1850 *wrinkled*	2.96:1
Yellow x *green* seeds	all *Yellow*	6022 *Yellow* : 2001 *green*	3.01:1
Purple x *white* petals	all *Purple*	705 *Purple* : 224 *white*	3.15:1
Inflated x *pinched* pods	all *Inflated*	882 *Inflated* : 299 *pinched*	2.95:1
Green x *yellow* pods	all *Green*	428 *Green* : 152 *yellow*	2.82:1
Axial x *terminal* flowers	all *Axial*	651 *Axial* : 207 *terminal*	3.14:1
Long x *short* stems	all *Long*	787 *Long* : 277 *short*	2.84:1

F_1: cross-pollination. F_2: self-pollination

The Mendelian Paradigms

- The inheritance of each trait is determined by "units" or "factors" that are passed on to descendants unchanged.
- An individual inherits one such "unit" from each parent for each trait.
- A trait may not show up in an individual but can still be passed on to the next generation.

The Mendelian Paradigms: Independent Assortment and Segregation

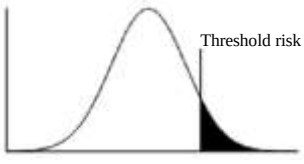


[http://en.wikipedia.org/wiki/]

Distribution of trait measures for polygenic additive trait (10 loci)

Continuous variation is a natural consequence of mendelian heredity for polygenic traits.

Threshold Model



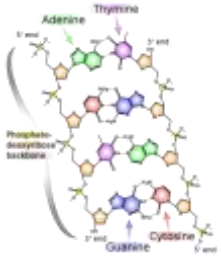
Population distribution of liability

The Structure and Flow of Genetic Information

Human Genome: physical parameters

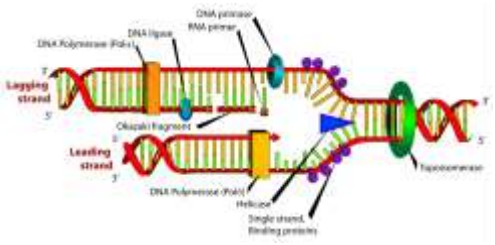
- number of base pairs	2.9 x 10^9 bp
- number of chromosomes	22 pairs of autosomes, plus XX or XY
- total linear length	± 2 m
(rotation 360º / 10 bp)	= 3.4 x 10^{-9} m
- width of the DNA molecule	2 x 10^{-9} m
- DNA mass per cell	7.1 x 10^{-12} g
- total number of genes	25 000 – 30 000 genes
- gene size	1 000 – 200 000 bp (typical: 30.000 bp)
mitochondrial genome	16 569 bp, 37 genes, no introns

DNA Molecular Structure



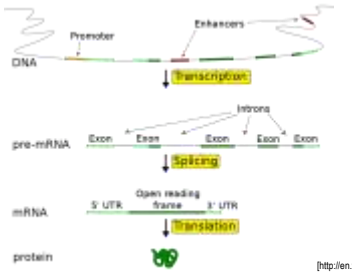
[http://en.wikipedia.org/wiki/]

DNA Replication



[http://en.wikipedia.org/wiki/]

Flow of Genetic Information



[http://en.wikipedia.org/wiki/]

Transcription and Translation

```
...G T G C A T C T G A C T C C T G A G G A G A A G...
...C A C G T A G A C T G A G G A C T C C T C T T C...   DNA
                                                      (transcription)
...G U G C A U C U G A C U C C U G A G G A G A A G...   mRNA
                                                      (translation)
...  V   H   L   T   P   E   E   K  ...
...(Val)-(His)-(Leu)-(Thr)-(Pro)-(Glu)-(Glu)-(Lys)...  Protein
```

The Genetic Code

	U	C	A	G	
U	Phe (F)	Ser (S)	Tyr (Y)	Cys (C)	U
	Phe (F)	Ser (S)	Tyr (Y)	Cys (C)	C
	Leu (L)	Ser (S)	*Stop*	*Stop*	A
	Leu (L)	Ser (S)	*Stop*	Trp (W)	G
C	Leu (L)	Pro (P)	His (H)	Arg (R)	U
	Leu (L)	Pro (P)	His (H)	Arg (R)	C
	Leu (L)	Pro (P)	Gln (Q)	Arg (R)	A
	Leu (L)	Pro (P)	Gln (Q)	Arg (R)	G
A	Ile (I)	Thr (T)	Asn (N)	Ser (S)	U
	Ile (I)	Thr (T)	Asn (N)	Ser (S)	C
	Ile (I)	Thr (T)	Lys (K)	Arg (R)	A
	Start / Met (M)	Thr (T)	Lys (K)	Arg (R)	G
G	Val (V)	Ala (A)	Asp (D)	Gly (G)	U
	Val (V)	Ala (A)	Asp (D)	Gly (G)	C
	Val (V)	Ala (A)	Glu (E)	Gly (G)	A
	Val (V)	Ala (A)	Glu (E)	Gly (G)	G

Genetic Variation of the Human Genome

The spectrum of variation in the human genome

Variation	Rearrangement type	Size range
Single base-pair changes	Single nucleotide variants, point mutations.	1 bp
Small insertions/deletions	Binary insertion/deletion events of short sequences (majority <10 bp in size).	1-50 bp
Short tandem repeats	Microsatellites and other simple repeats.	1-500 bp
Fine-scale structural variation	Deletions, duplications, tandem repeats, inversions.	50 bp to 5 kb
Retroelement insertions	SINEs, LINEs, LTRs, ERVs.	300 bp to 10 kb
Intermediate-scale structural variation	Deletions, duplications, tandem repeats, inversions.	5 kb to 50 kb
Large-scale structural variation	Deletions, duplications, large tandem repeats, inversions.	50 kb to 5 Mb
Chromosomal	Euchromatic variants, large cytogenetically visible deletions, duplications, translocations, inversions and aneuploidy.	~5 Mb to entire chromosomes

Sharp AJ, Cheng Z, Eichler EE. Structural Variation of the Human Genome. Annu. Rev. Genomics Hum. Genet. 2006. 7:407–442.

Molecular Variation

- **Single nucleotide polymorphisms/variants**
  - make up ~90% of all human genetic variation
  - occur every 100 to 300 bp; total >10 millions SNPs
  - 2/3 involve the replacement of cytosine with thymine (C>T)
- **Copy number polymorphisms/variants**
  - copy number change involving a DNA fragment that is ~1 kb or larger
  - 1,447 copy number variable regions identified in the human genome
  - cover 360 Mb (12% of the genome)
  - ~0.4% of the genomes of unrelated people typically differ with respect to copy number

Polymorphisms are variations observed in >1% of the population.

Chromosomal Heteromorphisms

- **prominent short arms of acrocentric chromosomes (13, 14, 15, 21, 22)**
  - –satellites, double satellites, stalks, double stalks
- **pericentric inversions**
  - –inv(2)(p11.2q13)
  - –inv(9)(p12q13)
  - –inv(Y)(p11.2q11.2)
- **variation in size (qh+, qh-) of heterochromatic regions of chromosomes 1, 9, 16, and Y**

Classification and Mechanisms of Genetic Diseases

Classification of Genetic Diseases

- resulting from germinal mutation/variation
  - chromosomal
  - single gene (mendelian; mitochondrial; etc.)
  - multiple genes (multifactorial; polygenic)
- resulting from somatic mutation
- resulting from interactions between germinal and somatic mutations

Adapted from McKusick VA: The Morbid Anatomy of the Human Genome. Medicine 1986; 65:1-33.

Single Gene Patterns of Inheritance

- mendelian
  - autosomal dominant
  - autosomal recessive
  - X-linked (dominant; recessive)
  - Y-linked
- mitochondrial
- triplet repeat amplification

Types of Mutations

- Human Gene Mutation Database®
  - Missense/nonsense
  - Splicing
  - Regulatory
  - Small deletions
  - Small insertions
  - Small indels
  - Gross deletions
  - Gross insertions
  - Complex rearrangements
  - Repeat variations

[http://www.hgmd.cf.ac.uk/ac/index.php]

Mechanisms of Dominance

- Molecular classification
  - haploinsufficiency
  - increased gene dosage
  - increased / ectopic mRNA expression
  - increased / constitutive protein activity
  - dominant negative
  - structural function
  - toxic protein
  - new protein

Wilkie AOM: The molecular basis of genetic dominance. J Med Genet 1994; 31:89-98.

Atypical Patterns of Inheritance

Inheritance pattern	Genetic mechanism	Disease example	Result or effect on the phenotype
Modifier gene	A second gene at a different locus may modify phenotype	Cystic Fibrosis	Modification of extent of lung disease, response to infection
Digenic inheritance	An inheritance mechanism resulting from the interaction of 2 nonhomologous genes	Deafness	Modification of the severity of deafness
Triallelic inheritance	Three mutations from genes at different loci segregate with expression of the disease	Bardet-Biedl syndrome	Mutations in a second locus affect inheritance pattern
Imprinting/opposite transcripts	A phenomenon whereby genes are differentially expressed according to parental origin	Beckwith-Wiedemann syndrome	Parent-specific patterns of inheritance

Gropman AL, Adams DR. Atypical Patterns of Inheritance. Semin Pediatr Neurol 2007;14:34-45.

OMIM
Online Mendelian Inheritance in Man

OMIM Statistics for March 10, 2010

Number of Entries

	Autosomal	X-Linked	Y-Linked	Mitochondrial	Total
• Gene with known sequence	12573	689	48	35	13345
▪ Gene with known sequence and phenotype	722	18	0	2	742
▸ Phenotype description, molecular basis known	2488	217	4	26	2737
▹ Mendelian phenotype or locus, molecular basis unknown	1618	141	5	0	1764
Other, mainly phenotypes with suspected mendelian basis	1008	174	2	0	1998
Total	18673	1122	59	63	**19917**

[http://www.ncbi.nlm.nih.gov/Omim/mimstats.html]

OMIM
Online Mendelian Inheritance in Man

OMIM Statistics for March 10, 2010

Synopsis of the Human Gene Map

Chr.	Loci	Chr.	Loci	Chr.	Loci
1	1214	9	865	17	718
2	779	10	452	18	176
3	655	11	774	19	780
4	470	12	650	20	510
5	580	13	224	21	143
6	737	14	381	22	306
7	544	15	367	X	695
8	447	16	482	Y	45
Total number of loci: **12394**					

[http://www.ncbi.nlm.nih.gov/Omim/mimstats.html]