What factors contribute to phenotypic variation?

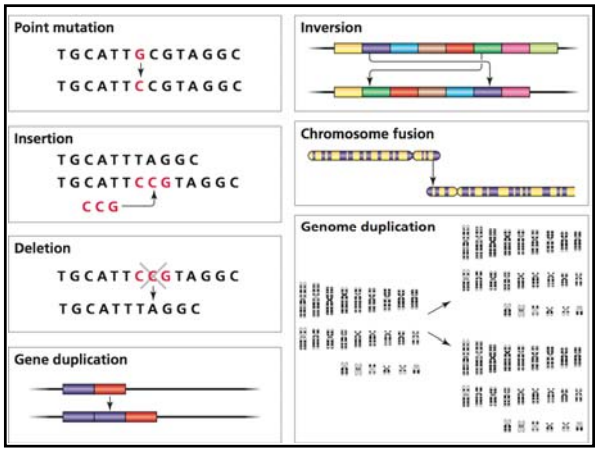
The world's tallest man, Sultan Kosen (8 feet 1 inch) towers over the world's smallest, He Ping (2 feet 5 inches).

WHERE DOES THE VARIATION COME FROM IN THE FIRST PLACE?

- The environment plays a significant role in the patterns of variation among individuals.

However,

- The ultimate source of variation that is the fuel for evolutionary change is **MUTATION.**



MAJOR SOURCES OF GENETIC CHANGE:
MUTATION "THE FUEL FOR EVOLUTION"

	Name	Description	Cause	Significance
1)	Point mutation	Base-pair substitutions in DNA sequences	Chance errors during DNA synthesis or during repair of damaged DNA	Creates new alleles
2)	Chromosome inversion	Flipping of a chromosome segment, so that the order of genes along the chromosome is altered	Breaks in DNA caused by radiation	Alleles inside the inversion are "locked together" into a unit
3)	Gene duplication	Duplication of a short stretch of DNA, creating an additional copy of a gene	Unequal crossing over during meiosis (see Fig. 4.3)	The "extra" gene is free to mutate and perhaps gain new function
4)	Polyploidy	Addition of a complete set of chromosomes	Errors in meiosis or (in plants) mitosis	Can create new species

The Phenotypic Effect of Mutations Depends on the Location of the Mutation

TABLE 5.3 Sources of Heritable Genetic Variation

Location of Mutation	Type of Mutation	Consequence for Gene Action
Coding region	Substitution, insertion, deletion, duplication.	Alters the **product** of the gene, and thus its function or activity.
cis-Regulatory Regions	Substitution, insertion, deletion, duplication that alters the binding affinity of promoters, activators, repressors, etc.	Alters the timing, location, or level of expression of the gene. Alters the developmental or environmental context in which the gene is expressed.
trans-Regulatory Regions	Mutation to **coding regions** of trans-acting factor	Alters the binding affinity and thus the activity of a promotor, activator, repressor, etc..
	Mutation to **cis-** or **trans-regulatory regions** of trans-acting factors	Alters where, when, or to what extent inhibitory, activating, or other trans-acting regulatory factors are expressed.
Physiological Pathways (e.g., hormones)	Mutation tMutations alter where, when, or how much an endocrine signal is produced	Alters the timing, location, or level of expression of the gene. Alters the developmental or environmental context in which the gene is expressed.

POINT MUTATIONS:

ACA ATG GTA CGA CAA

↓

ACA ATT GTA CGA CAA

- Changes in the nucleotide sequence can alter the amino acid sequence and change protein structure **OR** introduce stop codons.
- Point mutations in regulatory regions can alter the timing and levels of gene expression.

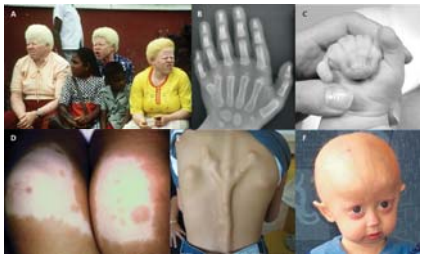
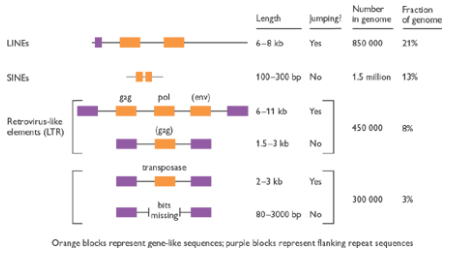


Fig. 5.14 in Z&E

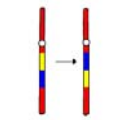
Transposable Elements: "Jumping Genes"

Barbara McClintock – Nobel Laureate 1983

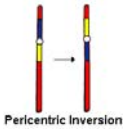


Orange blocks represent gene-like sequences; purple blocks represent flanking repeat sequences

Chromosomal Inversions

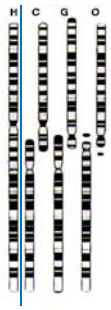


Paracentric Inversion



Pericentric Inversion

Chromosomal Fusions



GENE DUPLICATION:

Table 4.3 Some gene families

In this table, the "Number of duplicate genes" column refers to the number of loci in various gene families. These loci are presumed to be the result of duplication events. They have high sequence homology, code for products with closely related functions, and are often clustered close to one another on the same chromosome.

Family	Number of duplicate genes
Loci found in many organisms	
Actins	5–30
Tubulins (*a* and *b*)	5–15
Myosin, heavy chain	5–10
Histones	100–1000
Keratins	> 20
Heat-shock proteins	3
Insects	
Eggshell proteins (silk moth and fruit fly)	> 50
Vertebrates	
Globins (many species)	
α-like	1–5
β-like	≥ 50
Ovalbumin (chicken)	3
Vitellogenin (frog, chicken)	5
Immunoglobulins, variable regions (many species)	> 500
Transplantation antigens (mouse and human)	50–100

THE FATE OF DUPLICATE GENES:

- Retain their original function and provide an additional copy of the parent locus.
- Accumulate point mutations and become functionless pseudogenes.
- Gain a new function through mutation and selection (neofunctionalization).
  - While Humans and chimpanzees are ~1-2% different at the nucleotide level they are more than 3% different in gene copy number variants (CNV). Within Human populations many disease phenotypes are linked to CNVs.

- Different classes of mutation occur at different rates in humans, and affect different proportions of the genome.

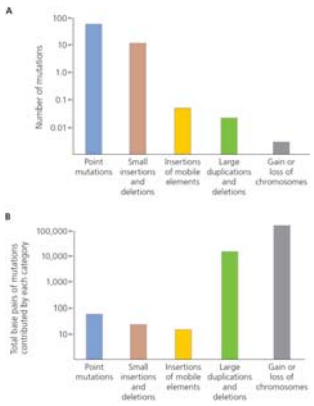


Fig. 5.15 Z&E

- **The genomic mutation rate appears to be roughly constant in haploid microbes and simple eukaryotes:**

ORGANISM	GENOME SIZE	PER BASE[1]	PER GENOME[1]
Phage M13	6.4×10^{3}	7.2×10^{-7}	0.0046
Phage lambda	4.8×10^{4}	7.7×10^{-8}	0.0038
Phage T2, T4	1.6×10^{5}	2.4×10^{-8}	0.0038
E. coli	4.7×10^{6}	5.4×10^{-10}	0.0025
Yeast	1.4×10^{7}	2.2×10^{-10}	0.0031
Neurospora	4.2×10^{7}	7.2×10^{-11}	0.0030

[1]per generation

- These results suggest that as genome size has increased the DNA replication – repair machinery has increased in efficiency.

Constancy of Mutation Rates?

From: J. W. Drake. 1991. Proc. Natl. Acad. Sci. USA 88:7160-7164.

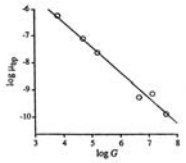


FIG. 1. Average mutation rate μ_{bp} per base pair as a function of genome size G in bp.

- The genomic deleterious mutation rate:

  ≈ 0.004/cell division in *E. coli*
  ≈ 1.5/generation in *D. melanogaster*

- High rates in flies and humans suggest **Drake's constancy hypothesis** cannot be extended to higher organisms.

THE MUTATION RATE IN HUMANS

- The mutation rate in males is on the order of 10*x* that in females, probably because of a higher number of cell divisions from zygote to gamete.

Female Cell divisions	≈ 24 (independent of age)
Male Cell Divisions	≈ 36 + ((Age-13) x 23)
	≈ 200 @ Age 20
	≈ 770 @ Age 45

- The male rate of **point** mutations is approx. 1.2×10^{-8} per base per generation, or approx 1×10^{-10} per cell division.
- The genomic mutation rate is approx. $(1.2 \times 10^{-8}) \times (3 \times 10^{9}$ bases/genome) ≈ 36.
- More than 6% of newly fertilized eggs carry a gross chromosomal abnormality.
  Approx. 5.5% of these terminate as spontaneous abortions.

FROM: J. F. Crow. 1993. Environ. Mol. Mutagenesis 21:122-129 & F. Vogel and R. Rathenberg. 1975. Adv. Human Genetics 5-223-318.

NATURE | NEWS

Fathers bequeath more mutations as they age

Genome study may explain links between paternal age and conditions such as autism.

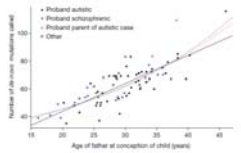
In the 1930s, the pioneering geneticist **J. B. S. Haldane** noticed a peculiar inheritance pattern in families with long histories of haemophilia. The faulty mutation responsible for the blood-clotting disorder tended to arise on the X chromosomes that fathers passed to their daughters, rather than on those that mothers passed down. Haldane subsequently proposed that **children inherit more mutations from their fathers than their mothers**, although he acknowledged that **"it is difficult to see how this could be proved or disproved for many years to come"**.

Haldane, J. B. S. *Ann. Eugen.* 13, 262–271 (1947).

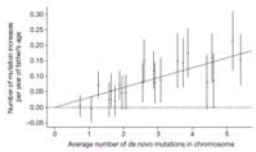
Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[2], Gunnar Sigurdsson[3], G. Bragi Walters[3], Stacy Steinberg[3], Hannes Helgason[3], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[3,4], Olafur Th. Magnusson[3], Unnur Thorsteinsdottir[1,3] & Kari Stefansson[1,3]

Mutations generate sequence diversity and provide a substrate for selection. The rate of ***de novo*** mutations is therefore of major importance to evolution. Here we conduct a study of genome-wide mutation rates by sequencing the entire genomes of 78 Icelandic parent–offspring trios at high coverage. We show that in our samples, with an average father's age of 29.7, the average ***de novo*** mutation rate is 1.20×10^{-8} per nucleotide per generation. Most notably, the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years. After accounting for random Poisson variation, father's age is estimated to explain nearly all of the remaining variation in the ***de novo*** mutation counts. These observations shed light on the importance of the father's age on the risk of diseases such as schizophrenia and autism.



Father's age and number of *de novo* mutations.



Effect of father's age by chromosome.

23 AUGUST 2012 | VOL 488 | NATURE | 471

DIRECTED MUTATION

- **Do mutations arise spontaneously OR in response to selective challenges???**

Luria & Delbruck

The Luria-Delbruck Fluctuation test (1943):

Pattern A: Mutation is Directed

Pattern B: Mutation is Random

Are Mutations Random?

- Cairns et al. (1988) exposed a Lac⁻ strain of *E. coli* to Lactose media and measured the rate of mutation to Lac⁺.

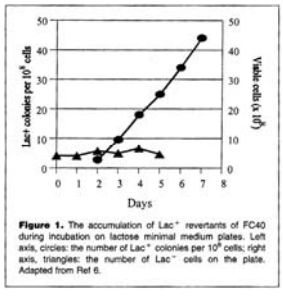


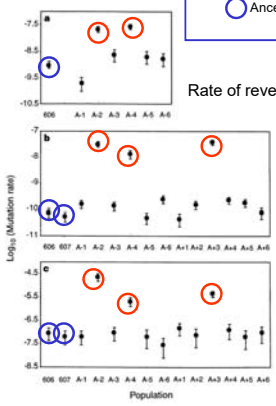
Figure 1. The accumulation of Lac⁺ revertants of FC40 during incubation on lactose minimal medium plates. Left axis, circles: the number of Lac⁺ colonies per 10^8 cells; right axis, triangles: the number of Lac⁻ cells on the plate. Adapted from Ref 6.

- **Is this evidence of "Adaptive Mutation"???**

FROM: Cairns, J., & P. L. Foster. 1991. Adaptive reversion of a frameshift mutation in *Escherichia coli*. *Genetics* 128:695-701

Mutation Rates after 10,000 Generations of Evolution

Ancestral Population High Mutation Lines



Rate of reversion from Ara$^-$ to Ara$^+$

Rate of mutation to nalidixic-acid resistance

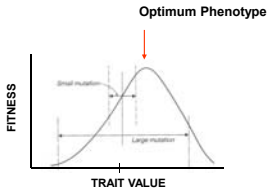
Rate of mutation to bacteriophage T5 resistance

FROM: Sniegowski et al. 1997. *Nature* 387:703-705

What Is Going On?

- Recent studies by Rosenberg and Foster suggest that alteration of the recombination-repair pathway is essential for this result.
- Starvation is mutagenic – either as an unavoidable consequence of physiological deterioration OR increasing the mutation rate may be adaptive in the sense that not mutating is certain death.
- These mutator strains may have a **short term** advantage coping with environmental stress but over the **long term** they will be at a selective disadvantage.

Mutational Effects: Fisher argued that mutations of small effect are more likely the fuel for evolution by natural selection.



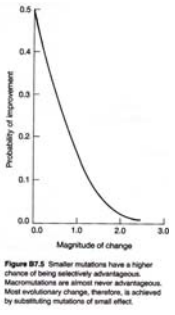


Figure B7.5 Smaller mutations have a higher chance of being selectively advantageous. Macromutations are almost never advantageous. Most evolutionary change, therefore, is achieved by substituting mutations of small effect.

Mutation Accumulation Experiments

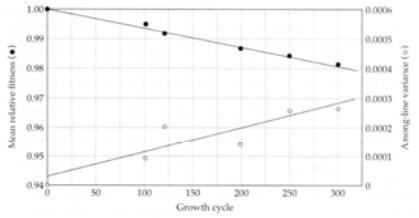


Figure 12.7 Similar plots to Figure 12.6 for 50 lines of the bacterium *E. coli* taken through daily single-cell bottlenecks for 300 days (with approximately 22 cell divisions per day). Here fitness is measured as the exponential rate of clonal expansion in liquid medium. (From Kibota and Lynch 1996.)

FROM: Lynch & Walsh 1998

Conclusions from mutation accumulation studies:

- The majority of spontaneous mutations have a **slightly** deleterious effect on fitness.
- The average effect of spontaneous deleterious mutations is a 1-2% decrease in fitness (Houle *et al.* 1997).

SUMMARY OF KNOWLEDGE ON MUTATION RATES

- The spectrum of mutations is enormous, ranging from chromosomal rearrangements (translocations and inversions) and duplications to insertion and excisions of transposable elements to single base substitutions, insertions, and deletions.
- The mutation rate is subject to evolutionary modification.
- The vast majority of mutations appear to be deleterious.
- Mildly deleterious mutations are much more common than lethals.
- The mutation rate per generation increases with the number of cell divisions --- in mammals, the point mutation rate is much higher in males than females.

SUMMARY OF KNOWLEDGE ON MUTATION RATES

- For polygenetic characters, the mutational rate of introduction of new variation is on the order of 0.1% to 1.0% of the standing variation.
- The adaptive value of mutations changes with the ecological circumstances.
- Mutations arise randomly with respect to their utility.
- The mutation rate can be modified greatly by the environment.