January, 2002
Genetics 453

Evolutionary Genetics

Population Genetics, part 2

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Mutation Rates

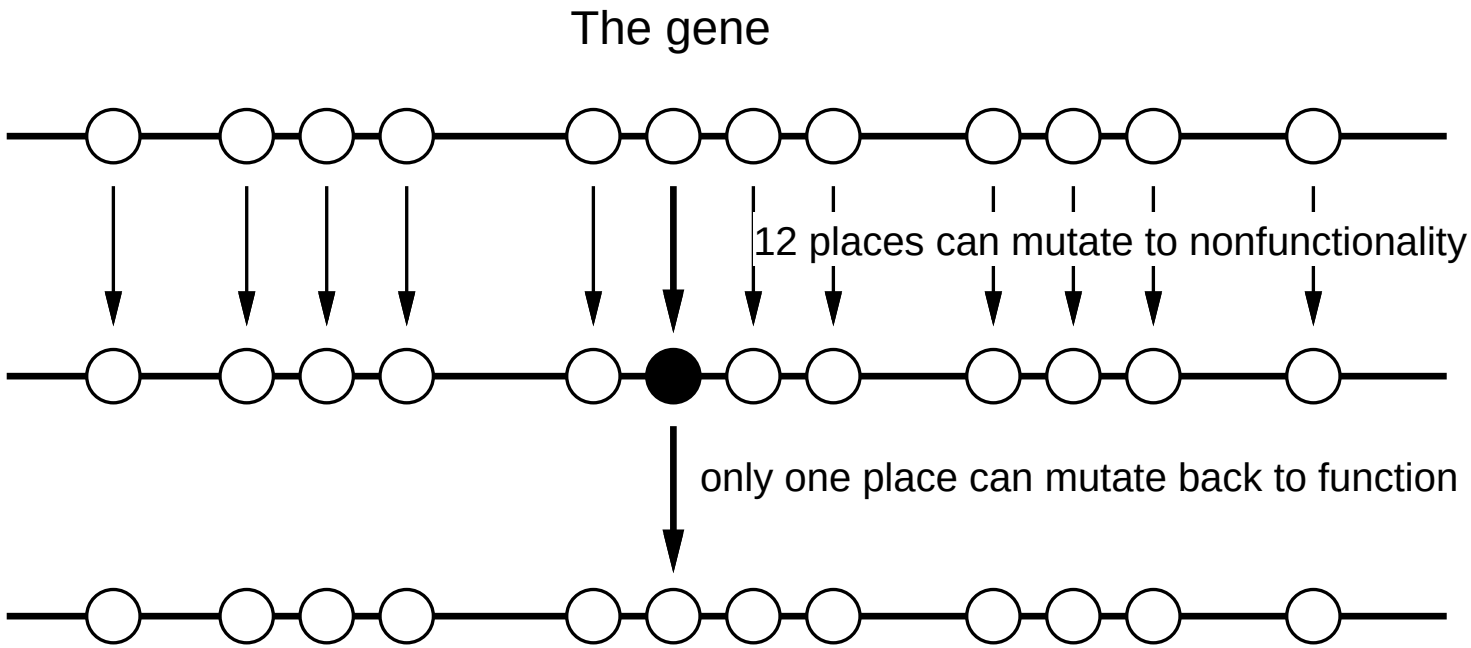
Coat color mutants in mice. From

Schlager G. and M. M. Dickie. 1967. Spontaneous mutations and mutation rates in the house mouse. *Genetics* **57:** 319-330

Locus	Gametes tested	No. of Mutations	Rate
Nonagouti	67,395	3	4.4×10^{-6}
Brown	919,619	3	3.3×10^{-6}
Albino	150,391	5	33.2×10^{-6}
Dilute	839,447	10	11.9×10^{-6}
Leaden	243,444	4	16.4×10^{-6}
Total	2,220,376	25	11.2×10^{-6}

Trait	Population examined	Mutation rate	Number of mutants/10^6 gametes	Authors
A. Autosomal mutations				
Achondroplasia	Denmark	1×10^{-5}	10	Mørch, corrected by Slat
	Northern Ireland	1.3×10^{-5}	13	Stevenson
	Germany (Reg. Bez. Münster)	$6–9 \times 10^{-6}$	6–9	Schiemann
Aniridia	Denmark	$2.9(–5) \times 10^{-6}$	2.9(–5)	Møllenbach, corrected by Penrose
	Michigan (U.S.A.)	2.6×10^{-6}	2.6	Shaw et al.
Dystrophia myotonica	Northern Ireland	8×10^{-6}	8	Lynas
	Switzerland	1.1×10^{-5}	11	Klein, corrected by Todorov et al.
Retinoblastoma	England, Michigan (U.S.A.), Switzerland, Germany	$6–7 \times 10^{-6}$	6–7	Vogel
	Hungary	6×10^{-6}	6	Czeizel et al.
	The Netherlands	1.23×10^{-5}	12.3	Schappert-Kimmijser et a
	Japan	8×10^{-6}	8	Matsunaga
	France	5×10^{-6}	5	Briart-Guillemot et al.
Acrocephalosyndactyly (Apert's syndrome)	England	3×10^{-6}	3	Blank
	Germany (Reg. Bez. Münster)	4×10^{-6}	4	Tünte and Lenz
Osteogenesis imperfecta	Sweden	$0.7–1.3 \times 10^{-5}$	7–13	Smårs
	Germany (Reg. Bez. Münster)	1.0×10^{-5}	10	Schröder
Tuberous sclerosis (epiloia)	Oxford Regional Hospital Board Area (G.B.)	1.05×10^{-5}	10.5	Nevin and Pearce
	Chinese	6×10^{-6}	6	Singer
Neurofibromatosis	Michigan (U.S.A.)	1×10^{-4}	100	Crowe et al.
	Moscow (U.S.S.R.)	$4.4–4.9 \times 10^{-5}$	44–49	Sergeyev
Polyposis of intestines	Michigan (U.S.A.)	1.3×10^{-5}	13	Reed and Neel
Marfan's syndrome	Northern Ireland	$4.2–5.8 \times 10^{-6}$	4.2–5.8	Lynas
Polycystic disease	Denmark	$6.5–12 \times 10^{-5}$	65–120	Dalgaard

Why mutants inactivating a functional gene will be more frequent than back mutations



function can sometimes be restored by a "second site" mutation, too

Sequence space

For sequences of length 1000, there are 3 X 1000 = 3000 "neighbors" one step away in sequence space

But there are 4^{1000} sequences, which is about 10^{602} in all !

No two of them are more than 1000 steps apart

Hard to draw such a space

How do we ever evolve? Woiuldn't it be impossible to find one of the tiny fraction of possible sequences that would be even marginally functional?

The answer seems to be that the sequences are clustered

An example of such clustering is the English language, as illustrated by a popular word game:

W	O	R	D
W	O	R	**E**
G	O	R	E
G	O	**N**	E
G	**E**	N	E

But the word BCGH cannot be made into an English word

There are also only a tiny fraction of all 456,976 four−letter words that are English words

But they are clustered, so that it is possible to "evolve" from one to another through intermediates

Estimation of a human mutation rate

By an equilibrium calculation. Huntington's disease. Dominant. Does not express itself until after age 40. Reduction in fitness maybe 2%.

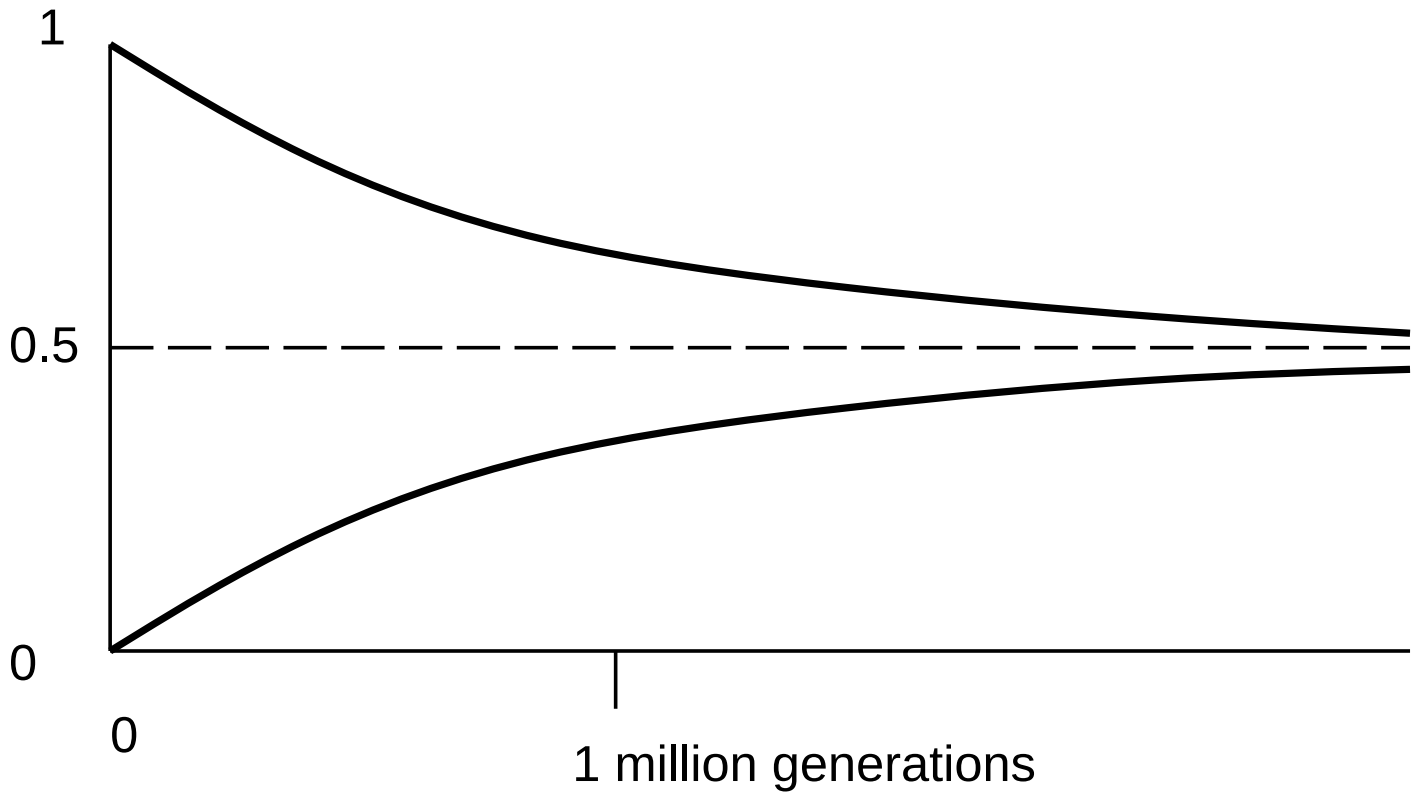
If allele frequency q, $2q(1-q)$ of everyone are carriers. 0.02 of these die. Each has half its copies the Huntington's allele. So as fraction of carriers $\simeq 1/100,000$, the fraction of all copies that are mutations that are eliminated is $0.00001 \times 1/2 \times 0.02 \simeq 10^{-7}$

If we are at equilibrium between mutation and selection, this is also the fraction of copies that have a new mutation.

Similar calculations can be done with recessive alleles.

Mutation as an evolutionary force

If we have two alleles A and a, amd mutation rate from A to a is 10^{-6} and mutation rate back is the same,



Mutation is critical in introducing new alleles but is very slow

This freeware-friendly presentation prepared with

- Linux (operating system)
- PDFLaTeX (mathematical typesetting and PDF preparation)
- Idraw (drawing program to modify plots and draw figures)
- Adobe Acrobat Reader (to display the PDF in full-screen mode)

(except that we had to use Microsoft Windows to project this as the X server I have in Linux is not too great)