B242 Exam 2001

Question 9 Model Answer:

9. a) Affected individuals of recessive allele CF occur at a frequency of 1 in 1984 individuals. Therefore, assuming HWE, genotypes should be CF-CF = q^2 = 1/1984, so CF frequency, q=0.02245.

b) Carrier frequency of CF^+-CF = 2(1-q)q = 0.04389

c) We are told that "affected individuals rarely survive to reproduce". This implies that the

fitness of CF-CF homozygotes is virtually nil, i.e. (1-t) . 0, so t . 1. Thus using q*=%(:/t), we obtain : . $t(q^*)^2 = 1 \times 1/1984 . 5 \times 10^{-4}$. This seems rather high, i.e. ***im***plausible for a mutation rate. Except for some microsatellite-disease causing alleles (which this is not).

d) i) Colonization of Scotland (and indeed Europe as a whole) might have involved a small number of founders who happened to carry the CF allele. The founders did well, and had many offspring, so that the resultant European population would have had high frequencies of the gene, as they do. There would of course have been selection against the homozygotes, but this selection is very weak, of the order of)q . $-sq^2$, which here means about -0.0005 per generation. Very roughly, this means it would take of the order of 20 generations to halve the frequency from 0.02 to 0.01. Take the generation time as 20 years; this means that to halve the frequency would take 400 years of selection.

ii) Given that p* = t/(s+t) at equilibrium, then here given that (1-0.02245) = 0.97755 = 1/(s+1). Thus s = (1/0.97755)-1 = 0.02297. The heterozygotes (with relative fitness 1) would have to be about 2.4% fitter than the CF^+-CF^+ homozygotes.

iii) This is more difficult. Under inbreeding alone, with no input of mutations, we wouldn't expect any CF alleles. So we have to assume some sort of mutation/selection balance. From (c), we might expect : $.5 \times 10^{-5}$ as a reasonably plausible, although somewhat high mutation

rate, so the equilibrium frequency q* . %0.00005 = 0.007071. Starting with this frequency, what level of inbreeding would be required to create 1/1984 sufferers in the population? The frequency of CF-CF homozygotes = q^2+Fpq under inbreeding at rate F (can be worked out from the formula given, or remembered from the lectures!). Here to produce the observed sufferer frequency therefore, 1/1984 = $(0.00707)^2$ +F(0.00707x0.99293), so F = 0.065.

So, which is more likely?

> i) Genetic drift seems likely during the various waves of colonization of Europe that have occurred during the last 50,000-10,000 years. However, we have had big populations for a long time, and such strong selection pressures in large populations against the high gene frequencies should have caused very strong reductions of allele frequencies over approximately 1,000 year timescale, so on balance the founder effect doesn't seem that likely.
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> ii) A fitness advantage of heterozygotes of the order of 2.4% would be very difficult to measure; one would have to do a lifetime study with several thousand individuals to

measure it. An additional complication is that the selection pressure that existed throughout history and prehistory to cause this high CF frequency may no longer exist; for example, one theory is that CF causes protection against cholera and other diarrhea-causing diseases, but cholera has been virtually absent this century in Britain.

iii) F=0.065 is quite a high rate of inbreeding, and in prehistoric conditions, not totally impossible, it is of the order of matings on average between first cousins once removed. However the mutation rate at the CF locus could be considerably lower, requiring a higher rate of inbreeding to maintain the observed 1/1984 sufferer rate. These days in European populations (even in Scotland!), inbreeding is more like $F<0.01$.

On balance, (ii) seems a most likely cause, because (i) and (iii) seem not very plausible at the magnitudes required to maintain such a high frequency of sufferers. However, what the selection pressure is, and why it only affects Europeans seems still somewhat mysterious.