Deacon's Challenge

No 179 - Answer

Recent work suggests that the incidence of Familial Hypercholesterolaemia (FH) in North-West Europe is approximately 1 in 200 live births. Using current techniques, the detection rate of disease-associated mutations in FH is approximately 50%. Calculate (a) the incidence of homozygous FH, and (b) the probability that the child of a proband with genetically-confirmed FH has homozygous FH.

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FH is an autosomal dominant disorder with homozygotes being more seriously affected than heterozygotes.

Let *A* be the dominant gene with frequency in the population *p*

Let *a* be the recessive gene with frequency in the population *q*

Therefore $p + q = 1$

If the Hardy-Weinberg equilibrium applies to the disorder then:

$$p^2 + 2pq + q^2 = 1$$

where p^2 is the incidence of homozygotes with FH, $2pq$ the incidence of heterozygotes and q^2 the incidence of individuals without the genetic defect.

As the disease associated mutations are only detected in a half of patients with FH and assuming the figure for their incidence is based on genetic testing, then the true incidence of FH will be twice 1 in 200 i.e. 1 in 100 or 0.01.

Presumably the incidence of 0.01 for FH in the population includes both homozygotes and heterozygotes. Therefore:

$$p^2 + 2pq = 0.01$$

Substituting this value into the Hardy-Weinberg equation enables calculation of *q*:

$$0.01 + q^2 = 1$$
$$q^2 = 1 - 0.01 = 0.99$$
$$q = \sqrt{0.99} = 0.9950$$

by difference $p = 1 - 0.9950 = 0.0050$

and $2pq = 2 \times 0.0050 \times 0.9950 = 0.00995$

a) The incidence of homozygous FH (i.e. *AA*) will be given by p^2

$p^2 = 0.005^2 =$ **0.000025**

or $1/0.000025 =$ **1 in 40,000**

b) The proband with FH must be either homozygous (*AA*) or heterozygous (*Aa*):

$$\text{Probability of } AA = \frac{\text{Incidence of } AA}{\text{Incidence of } AA + Aa} = \frac{p^2}{p^2 + 2pq}$$

$$= \frac{0.000025}{0.000025 + 0.00995} = \frac{0.000025}{0.009975} = 0.002506$$

And the probability of *Aa* = 1 - 0.002506 = 0.9975 (4 sig figs)

The probability that the proband donates the dominant gene is the sum of the probabilities of the gene arising from a homozygote or heterozygote *in an individual with known FH*:

Probability of donating *A* =

(Probability of *AA* genotype) + (Probability of *Aa* genotype x 0.5)

$= 0.002506 + (0.9975 \times 0.5)$
$= 0.002506 + 0.49875$
$= 0.501$ (to 3 sig figs)

The probability of the proband's partner donating the dominant gene is the probability of A arising from either *AA* or *Aa* genotype *in the general population*:

Probability of donating *A* =

(Probability of *AA* genotype) + (Probability of *Aa* genotype x 0.5)

$p^2 + 2pq \times 0.5$
$= 0.000025 + (0.00995 \times 0.5)$
$= 0.000025 + 0.004975$
$= 0.0050$

The probability of a child having homozygous FH is the product of the probability of each parent donating the dominant gene.

Probability of homozygous FH (*AA*) = 0.501 x 0.0050 = **0.002505** (2 sig figs)

or $1/0.002505 =$ approx. **1 in 400**

Question 180

It has been suggested that measurement of Calprotectin in faeces can be used to distinguish between Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS). Diagnosis of IBD requires colonoscopy, diagnosis of IBS does not.

At present, all patients referred to your local Gastroenterologists' clinic with either IBS or IBD undergo colonoscopy. They wish to restrict colonoscopy to patients with a faecal calprotectin > 50 µg/g. Calculate the anticipated cost saving/patient of this strategy.

NB: At present, 48% of patients referred to the clinic are found to have IBD at colonoscopy.

Studies indicate a cut-off value of 50 µg/g faeces has a sensitivity of 99% and specificity of 74% for distinguishing between IBS and IBD in the out-patient setting.

The total cost of a faecal calprotectin assay has been estimated at £22.79. The cost of a colonoscopy is £750 (for the purposes of this question, you should ignore the possible costs of any complications arising from colonoscopy)

(Broadly based on NICE DG11; October 2013)

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