Deacon's Challenge

No 161 - Answer

A 65-year old married woman in good health has just discovered that her brother is homozygous for the C282Y haemochromatosis gene mutation. Her sister has been tested and has the normal genotype. Her own genotype is as yet unknown. The population gene frequency for C282Y is 8%, and the lifetime penetrance is estimated to be 30%.

Calculate the probability of each of the possible genotypes in both the woman and her partner, and use these data to determine the probability that their child will develop clinical haemochromatosis. You should ignore any possible contribution from any other genetic loci associated with haemochromatosis.

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It is only possible for her brother to be a homozygous for the C282Y gene mutation (C/C) and her sister a normal genotype (N/N) if both parents are heterozygous (N/C).

Each parent has an equal chance of producing gametes that are either normal (N) or mutated (C). Therefore the probability of each possible genotype for the patient can be calculated:

Patient	N/N	P = 0.5 x 0.5 = **0.25**
	N/C	P = (0.5 x 0.5) + (0.5 x 0.5) = **0.5**
	C/C	P = 0.5 x 0.5 = **0.25**

(Note that even though the patient is clinically unaffected it is still possible that she could have the CC genotype because the penetrance of haemochromatosis is only 30%.)

Since no information is available for her partner it can be assumed that he has the same risk as the general population. The population gene frequency is 8% and the probability of each genotype can be calculated from the Hardy-Weinberg formulae:

$$p + q = 1$$

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

where p = frequency of the dominant allele

q = frequency of the recessive allele

Since the frequency of the recessive gene (C) is 8% it follows that $q = 0.08$ and $p = 1 - 0.08 = 0.92$ allowing calculation of the probability for each genotype in her partner:

N/N = p^2 = 0.92^2 = **0.8464**

N/C = $2pq$ = 2 x 0.92 x 0.08 = **0.1472**

C/C = q^2 = 0.08^2 = **0.0064**

Their child can only develop haemochromatosis if he/she is homzygous for the mutation (C/C) which can only arise by inheritrance of the mutated gene (C) from each parent which can only occur if both parents are either C/C or N/C. The probability of each event occurring is the product of the probabilities of each genotype from each parent:

Patient C/C and Partner C/C	= 0.25 x 0.0064	= 0.0016
Patient C/C and Partner N/C	= 0.25 x 0.1472	= 0.0368
Patient N/C and Partner C/C	= 0.5 x 0.0064	= 0.0032
Patient N/C and Partner N/C	= 0.5 x 0.1472	= 0.0736

(Note that as the normal (N/N) was excluded these probabilities do not add up to 1).

The probability of transmission of the homzygous genotype for haemochromatosis for each of these possible crosses is then calculated:

Patient C/C and Partner C/C	= 1 x 1	= 1.0
Patient C/C and Partner N/C	= 1 x 0.5	= 0.5
Patient N/C and Partner C/C	= 0.5 x 1	= 0.5
Patient N/C and Partner N/C	= 0.5 x 0.5	= 0.25

The probability that her child is C/C is the sum of the probability of each cross multiplied by the probability that the cross will result in C/C:

(0.0016 x 1) + (0.0368 x 0.5) + (0.0032 x 0.5) + (0.0736 x 0.25)

= 0.0016 + 0.0184 + 0.0016 + 0.0184 = 0.04 (4%)

The risk of clinical disease is the probability of the affected genotype (0.04) multiplied by penetrance (30% or 0.3):

Risk of clinical haemochromatosis = 0.04 x 0.3 = **0.012 (or 1.2%)**

Question 162

Current guidelines indicate that a patient with familial hypercholesterolaemia who fails to achieve a 50% reduction in LDL-cholesterol concentration compared to the pre-treatment value should be referred for specialist management. In your laboratory, LDL-cholesterol is calculated using the Friedewald equation and the results of total cholesterol, triglycerides and HDL-cholesterol.

A patient has a pre-treatment LDL-cholesterol of 12.2 mmol/L. Calculate the value following treatment that would allow you to confirm a 50% fall in the true value with greater than 95% probability.

Current IQC performance shows CVs of: total cholesterol 2.9% at 7.0 mmol/L, HDL cholesterol 2.7% at 1.5 mmol/L, and triglycerides 2.5% at 1.6 mmol/L.

Table of *z*-distribution:

P(%)	10	5	2	1	0.2	0.1
z	1.65	1.96	2.33	2.58	3.09	3.29

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