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Frequency of carriers of cystic fibrosis gene among patients with myeloid malignancy and melanoma

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Cystic fibrosis is an autosomal recessive disease with a prevalence of carriers of about 5% and an overall incidence in white populations of 1 in 2000 live births. The cystic fibrosis gene has been cloned and sequenced, and a deletion ($\Delta F508$) that causes the loss of a phenylalanine residue at amino acid position 508 has been mapped.¹ This deletion accounts for 74% of carriers in Britain.²

In a preliminary report of an epidemiological survey of families affected by cystic fibrosis an association between putative carrier status for cystic fibrosis and leukaemia (most notably acute myeloid leukaemia) was found.^{3,4}

To test this association we studied the frequency of $\Delta F508$ in DNA from patients with acute myeloid leukaemia, the myelodysplastic syndrome, and malignant melanoma (as a solid tumour control) and from normal subjects.

Patients, methods, and results

Normal DNA was obtained at random from healthy donors from the blood transfusion service. Donors were screened according to the blood service's protocols, which included an extensive questionnaire, interview by the attending doctor, and check of haemoglobin concentrations and blood pressure. These samples were not consecutive. Samples from patients with acute myeloid leukaemia and the myelodysplastic syndrome were obtained from the department of

haematology and from those patients with melanoma from the department of surgery and subsequent follow up clinics. The patients were selected at random and the sample size was determined by the availability of material.

The samples were either peripheral blood, bone marrow, histological specimens, fresh washes of the buccal mucosa, or paraffin embedded tissue blocks. They were screened for $\Delta F508$ by using a modified polymerase chain reaction procedure and polyacrylamide gel electrophoresis. Direct sequencing of the products of the polymerase chain reaction confirmed the published sequences for the wild type and mutated alleles.

The table shows the results of the screening for the deletion. The expected number of carriers of $\Delta F508$ were estimated on the basis of the putative gene frequency in the population, which is 74% of $1/20=1/27$. Most of the groups studied had the normal expected frequency for carriers. Except for patients with melanomas, the differences found were not significant.

Unexpectedly, no carriers were found among 166 patients with melanoma. This differed significantly from the eight carriers found among 162 normal subjects ($p=0.007$, Fisher's exact two tailed test). In 91 of the patients with melanomas the constitutional genotype was confirmed by analysis of tissue from adjacent skin, blood, or buccal mucosal cells. In a genetic survey of first and second degree relatives of patients with cystic fibrosis two skin cancers were found. Both of these were basal cell carcinomas not melanomas, although among the number of patients studied the expected frequency of melanoma was less than one ($3000/10\ 000=0.3$).

Comment

This study shows that carriers of $\Delta F508$ may be protected from developing melanoma. The finding of a single carrier in the group with naevus suggests that cell lineage specificity is not a possible explanation for this finding. The case for leukaemias has yet to be proved: to reach significance with a carrier to non-carrier ratio of 2:1 roughly 600 patients in each leukaemic group would have to be analysed.

Carriers of one cystic fibrosis gene show no symptoms of the disease. This has led to the suggestion that heterozygosity for cystic fibrosis confers some form of biological advantage that has allowed the potentially lethal gene to be retained in the population at a high frequency. The incidence of melanoma in the United Kingdom, however, is 10 in 100 000, and therefore it does not seem that protection against only melanoma

Carriers of $\Delta F508$ in patients with and without malignancy

	No studied	No of $\Delta F508$ carriers		Odds ratio (95% confidence interval)*
		Expected	Observed	
Patients with:				
Myelodysplastic syndrome	159	6	7	0.89 (0.28 to 2.77)
Acute myeloid leukaemia	137	5	7	1.04 (0.33 to 3.25)
Naevus	20	1	1	1.01 (0.12 to 8.55)
Melanoma	166	6	0†	0 (0 to 0.64)
Normal subjects	162	6	8†	

*Using Cornfelds method.

†Comparison of patients with melanoma and normal subjects, $p=0.007$ (Fisher's exact two tailed test).

by heterozygosity for cystic fibrosis would confer biological advantage. The $\Delta F508$ is most common in white populations in the United Kingdom, United States, and The Netherlands but has a greatly reduced incidence in southern European populations⁵ and in black and Mongoloid populations. Noticeably, fair skinned people are the most susceptible to melanoma and so would benefit the most from the possibly protective heterozygous state.

Our finding of an inverse association between being a carrier of $\Delta F508$ and melanoma was unexpected. It suggests that the presence of a genetic marker (or gene defect) may protect against melanoma.

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Suicide among men in the highlands of Scotland

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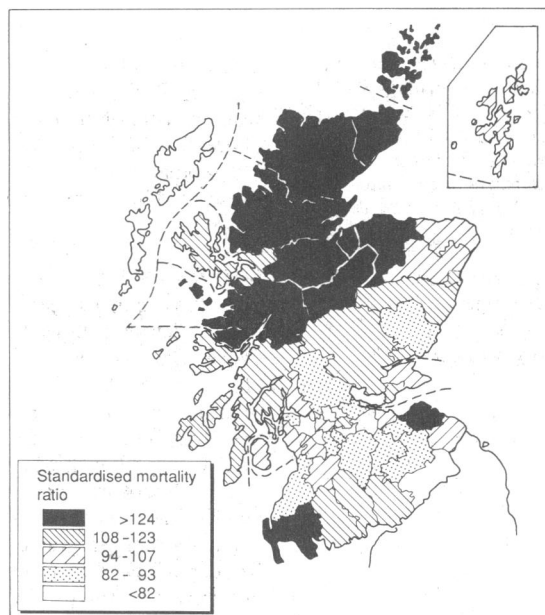
Suicide in Scotland has attracted attention because of an unexplained, rapid rise in the rates among men.¹ A recent study found no association between suicide rates and levels of unemployment.² This was unexpected as unemployment is known to be associated with many measures of social deprivation that might themselves be associated with high suicide rates.³ I therefore studied the geographical distribution of suicide in Scotland.

Subjects, methods, and results

Data on deaths from suicide (ICD (ninth revision) codes 950-959), accidental poisoning (ICD codes 850-869), and deaths undetermined, whether accidentally or purposely inflicted (ICD codes 980-989), during 1974-86 for the 56 local government districts were obtained as described previously.¹ Population data were obtained from the annual report of the registrar general (Scotland) for 1981. Standardised mortality ratios were calculated for each sex as described by Armitage⁴ by using five year age specific mortality rates and population data.

A total of 4054 men died by suicide during 1974-86. Standardised mortality ratios for local government districts covered a fivefold range from 39 to 226 (the value for Scotland as a whole is defined as 100). The figure shows that during 1974-86 almost all the highest rates of suicide among men occurred in northern Scotland. All eight districts in the highland region had standardised mortality ratios above 120, and there were 95 more deaths from suicide than expected in this region. With two exceptions, low rates of suicide were found exclusively in the central belt of Scotland. This distribution was not simply due to chance variation in the rates because the same pattern was found when the districts with appreciably raised or lowered standardised mortality ratios were mapped (data not shown). Furthermore, the pattern was stable over time: when standardised mortality ratios were calculated separately for 1974-9 and 1982-6 six of the highland districts had standardised mortality ratios above 120 for both periods and nine of the central belt districts had standardised mortality ratios below 80 for both periods.

An analysis of the methods of suicide showed that suicides by drowning and hanging followed the gradient for all suicides most closely, but the



Geographical distribution of mortality from suicide among men in Scotland by local government district during 1974-86. Each range represents a fifth of distribution

pattern for the other methods was inconsistent. The geographical distribution could not be explained by regional differences in notification of suicide: when deaths from accidental poisoning and those that were undetermined were aggregated with the deaths from suicide the pattern was preserved.

The range in standardised mortality ratios for suicide among women (41 to 147) was less than that among men, and the association between the rates in the two sexes was weak (correlation coefficient $r=0.184$, $p>0.2$). The geographical distribution of suicide among women was also harder to interpret, partly because their lower mortality rates were subject to much more sampling variation. Thus only three districts had appreciably raised standardised mortality ratios, two in the north of Scotland and one in the central belt. A map of standardised mortality ratios for women confirmed this weak and inconsistent pattern (data not shown).

Comment

The finding of a cluster of high mortality from suicide among men in the districts in the highlands of Scotland was unexpected. The districts with low mortality were in the central belt of Scotland, which is associated with high population density, heavy industry, and social disadvantage. Mental illness is by