

Prevalence of cystic fibrosis mutations in the Grampian region of Scotland

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Abstract

We have identified all known sufferers of cystic fibrosis (CF) alive in the Grampian region, north east Scotland, on 1 January 1989. DNA samples were obtained for a prevalence study of the common mutations with near to complete ascertainment. A relatively high prevalence of the $\Delta F508$ mutation was found (82%), with one of four mutations being present on 92% of CF chromosomes. The high prevalence of these four easily detectable mutations in Grampian has local implications for genetic counselling, the efficacy of population carrier screening, and the usefulness of mutation analysis in cases where the diagnosis of CF is in doubt.

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We have identified all known cystic fibrosis (CF) sufferers alive in the Grampian region, Orkney, and Shetland (population 545 000) on 1 January 1989 as part of a population study of north east Scotland.

Patients were identified from all possible sources including clinicians, local registers, and national computerised records. CF diagnosis required relevant clinical features and three positive sweat tests. DNA samples were obtained and tested for the mutations listed in the table using standard methods.¹⁻³

A life table of age at diagnosis was constructed and used to estimate the proportion of cases alive on 1.1.89 whose diagnosis had not been made by 1.7.92 (17%). Results of mutation analysis are presented in the table. The proportion of $\Delta F508$ CF chromosomes found (82%) was significantly greater than that reported previously for Scotland¹ (71%, 95% confidence intervals 0.02 and 0.18).

The $\Delta F508$ frequency among CF chromosomes of Grampian origin (grandparents) was not significantly different from that among chromosomes from outside Grampian (50/64 *v* 21/24, $\chi^2 = 0.98$).

Frequency of CF mutations in Grampian on 1.1.1989.

Mutation	No of CF chromosomes	Proportion (%)
$\Delta F508$	96	82.1
G551D	8	6.8
G542X	2	1.7
$\Delta 1507$	1	0.85
1717-1G-A	1	0.85
621 + 1G-T	1	0.85
R553X	1	0.85
R560T	0	—
R117H	0	—
No mutation identified	7	6.0
Total	117	100.0

The calculated point prevalence, adjusting for cases in whom a diagnosis has not yet been made, was much higher (1/7100) than that reported for Britain (1/11 400⁴), as was the calculated incidence (1/2260 *v* 1/2500). These findings may reflect a higher gene frequency in Grampian, longer survival, or merely better ascertainment.

The proportion of CF chromosomes carrying the $\Delta F508$ mutation in Grampian is significantly higher (82%) than that reported previously for a Scottish population (71%).¹ That population was largely from south east Scotland, so both these frequencies fit the north west-south east cline in $\Delta F508$ frequency across Europe.⁵ Alternatively, our findings may reflect a founder effect, as has been shown in Brittany (80%)⁶ and the Basque country (87%).⁷

However, the origin of chromosomes in our study has no effect on $\Delta F508$ frequency so our findings may reflect virtually complete ascertainment and careful exclusion criteria. All the CF chromosomes carrying G551D were of Grampian origin, which is in keeping with the hypothesis that it is a Celtic mutation.⁶

All CF patients in Grampian have at least one identifiable CF mutation, so we predict only 1 in 277 patients would have no detectable mutations (Hardy-Weinberg). This may be helpful in cases where the diagnosis of CF is in doubt.

Testing for four common mutations simultaneously ($\Delta F508$, G551D, G542X, and 621 + 1G-T)² can detect 92% of Grampian carriers, making carrier screening more efficient than might be expected from other studies (84% Scottish study,¹ 83% Welsh study⁸). Eighty-three percent of carrier couples are identified in contrast to 71% calculated from the Scottish study¹ and 69% from the Welsh study.⁸ When the partner of a carrier tests negative for the above mutations, the couple's residual risk of having an affected child is of the order of 1/1200 compared to 1/520.

Local knowledge of the prevalence of CF mutations is essential for good genetic counselling for CF families and before considering any population for screening. Any cost-benefit analysis of screening produced by studies from other areas should be considered in the context of the local prevalence of mutations.

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