Maternal gene effect in neurofibromatosis 2: fact or artefact?

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EDITOR—Neurofibromatosis 2 (NF2) is a rare autosomal dominant disease that is characterised by benign nervous system tumours, skin lesions, and ocular abnormalities.^{1–3} Two studies have found that NF2 patients with a family history of the disease and with maternal inheritance have more severe disease than inherited cases with paternal inheritance. Kanter *et al*⁴ noted that patients with maternal inheritance had an earlier age at onset and Evans *et al*⁵ found that patients with maternal inheritance had both an earlier age at onset and an earlier age at death. In both studies, the mean age at onset was 18 years with maternal inheritance and 24 years with paternal inheritance.

These results require confirmation for several reasons. First, Parry *et al*⁶ found identical mean ages at onset (22.8 years) in symptomatic NF2 patients with paternal or maternal inheritance. Second, these studies were based on relatively small numbers of patients. Kanter *et al*⁴ studied 38 inherited cases, Evans *et al*⁵ studied 56 inherited cases, and Parry *et al*⁶ studied 36 inherited cases; 66% of the patients in Kanter *et al*⁴ and 64% in Evans *et al*,⁵ but only 39% in Parry *et al*,⁶ had maternal inheritance. Third, in examining the effect of maternal inheritance on disease severity, these studies reported only age at onset (and age at death in Evans *et al*⁵) as indices of disease severity. In addition to age at onset or age at diagnosis, NF2 disease severity is defined by the number of non-vestibular schwannoma cerebral tumours and of spinal tumours.⁶ Fourth, none of the studies examined potential confounding factors (such as type of treatment centre and constitutional NF2 mutation type) that can affect age at onset, age at diagnosis, or mortality. NF2 patients who are treated at non-specialty centres have higher odds of death than those who are treated at specialty centres, and NF2 patients with missense mutations have lower odds of death than those with nonsense or frameshift mutations.⁷ Genotype-phenotype correlation studies have found that NF2 patients with constitutional NF2 missense

mutations or large deletions generally have mild disease, those with splice site mutations have variable disease severity, and those with nonsense or frameshift mutations have severe disease.^{8–11}

We reassessed the question of maternal gene effect in NF2 with a larger number of patients and with consideration of potential confounders. We used data from the United Kingdom NF2 Registry, based in the Department of Medical Genetics, St Mary's Hospital, Manchester. Patients are ascertained by contacting neurosurgeons, neurologists, otolaryngologists, paediatricians, dermatologists, and geneticists throughout the United Kingdom, augmented in the North West Region by the Regional Cancer Registry. As of 15 September 2000, the registry had data on 140 inherited cases (85 with maternal inheritance and 55 with paternal inheritance, including the 56 inherited cases previously reported by Evans *et al*⁵). All patients met the Manchester clinical diagnostic criteria for NF2⁵ or had identified constitutional NF2 mutations.

For univariate analyses, the two tailed *t* test was used for age variables, the χ^2 test for discrete variables (for example, distribution of mutation types), and life tables for mortality analysis. Multivariate analyses were used to examine the independent effects of covariates (linear regression for age variables and the Cox proportional hazards model for mortality analysis). Because age at onset and age at diagnosis are highly correlated (in the present study, $r^2 = 0.78$, $p < 0.001$), separate multiple linear regressions were done with each age variable as the outcome. *p* values ≤ 0.05 were considered to be statistically significant.

In univariate comparisons of patients with maternal and paternal inheritance, patients with maternal inheritance were treated slightly more frequently at non-specialty centres (75% versus 62%, $p = 0.10$) and had a slightly lower mean age at onset (23.1 years versus 25.5 years, $p = 0.30$). The distribution of constitutional NF2 mutation types varied significantly

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Table 1 Results of multiple linear regressions

Covariate	Outcome			
	Age at onset (y)		Age at diagnosis (y)	
	b (95% CI)	p	b (95% CI)	p
Type of treatment centre (specialty compared to non-specialty)	−4.7 (−9.8,0.4)	0.07	−10.5 (−16.0,−5.0)	<0.001
Constitutional NF2 mutation type (compared to nonsense or frameshift)				
Splice site	0.1 (−6.8,7.0)	0.99	2.4 (−5.4,10.2)	0.54
Missense	17.2 (9.6,24.8)	<0.001	24.1 (15.3,32.9)	<0.001
Large deletions	7.1 (0.5,13.6)	0.04	10.8 (3.4,18.2)	0.01
Unidentified	5.3 (−1.6,12.2)	0.13	6.4 (−1.6,14.4)	0.12

Table 2 Results of multivariate Cox proportional hazards model

Covariate	Odds of death (95% CI)	p
Type of treatment centre (specialty compared to non-specialty)	0.05 (0.00, 0.45)	0.008
Age at diagnosis (per year)	0.84 (0.78, 0.90)	<0.001
Intracranial meningiomas (per tumour)	1.27 (1.06, 1.51)	0.008

Age at diagnosis was used instead of age at onset because tumour burden was usually evaluated at diagnosis.

by mode of inheritance ($p=0.03$); in particular, patients with maternal inheritance had a lower proportion of missense mutations (7% versus 24%). Patients with maternal inheritance had significantly higher mortality ($p=0.02$).

In the multiple linear regression analyses, age at onset and age at diagnosis did not vary significantly with mode of inheritance (table 1). Patients with missense mutations and large deletions had significantly higher ages at onset and diagnosis than patients with nonsense or frameshift mutations. Patients treated at specialty centres had lower age at onset and significantly lower age at diagnosis than patients treated at non-specialty centres. In the multivariate Cox proportional hazards model, the odds of death did not vary significantly with mode of inheritance or type of constitutional *NF2* mutation (table 2). The odds of death varied significantly with type of treatment centre, age at diagnosis, and number of intracranial meningiomas.

The results of this study, the largest to date, are consistent with previous genotype-phenotype correlation studies in *NF2*,⁸⁻¹¹ but do not support maternal inheritance as an independent correlate of disease severity in *NF2*. The effects of constitutional *NF2* mutation type and treatment in specialty centres could not be examined in the earlier, more limited data of Kanter *et al.*,⁴ Evans *et al.*,⁵ and Parry

*et al.*⁶ Potential confounders should be routinely examined when outcomes that can be affected by multiple factors are being studied.

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Familial medullary thyroid carcinoma and prominent corneal nerves associated with the germline V804M and V778I mutations on the same allele of *RET*

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EDITOR—Germline mutations in the *RET* proto-oncogene are associated with multiple endocrine neoplasia (MEN) type 2A, 2B, and familial medullary thyroid carcinoma (FMTc). MEN 2A is characterised primarily by medullary thyroid carcinoma (MTC), parathyroid hyperplasia, and pheochromocytoma. MEN 2B has additional stigmata including a marfanoid habitus, mucosal neuromas, and corneal nerve thickening. In FMTc, the

only lesion present is MTC. Although characteristic of MEN 2B, prominent corneal nerves have been noted in subjects with MEN 2A.

Case reports

We have studied a family presenting with MTC and corneal nerve thickening (CNT), but no evidence of MEN 2 related disease outside the thyroid gland (fig 1). The proband (III.1) was found to have prominent corneal nerves on