

# Do familial neural tube defects breed true?

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## Abstract

**The tendency for sibs affected by non-syndromal neural tube defect (NTD) to have the same type of lesion was assessed retrospectively in a series of 66 affected sibships from the west of Scotland. Different schemes were used to classify the lesions: in the simplest classification into either anencephaly (including anencephaly-spina bifida) or spina bifida there was a tendency for spina bifida to breed true. More detailed description of the NTD in 48 sibships permitted classification according to location on the neuraxis; in this scheme sibs had dissimilar lesions. In 48 sets of affected sibs the lesions were separable into *high* NTD, which had involvement above vertebral level T12, and *low* NTD, which did not extend above T12. *Low* lesions comprised a minority of the total and each one occurred in a sibship with a *high* lesion. These results do not support the idea that NTDs occurring above and below vertebral level T12 have a different genetic basis.**

Data on the genetics and epidemiology of neural tube defects (NTD) are abundant, well documented, and largely unexplained.<sup>1</sup> Nevertheless, recent observations have stimulated new suggestions concerning genetic and embryological mechanisms of NTD. Two studies from North America paid detailed attention to the site of the NTD on the neuraxis and found complete concordance between affected sibs for the level of lesion after applying a broad classification which distinguished NTD with involvement above vertebral level T12 (*high*) from NTD below that level (*low*).<sup>2,3</sup> Moreover, one of these studies observed that the recurrence risks for these two types of NTD were significantly different.<sup>3</sup>

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Not every series has shown concordance between affected sibs for the level of NTD. In an epidemiological study of NTD in Newfoundland, four out of 11 sib pairs were discordant for the level of lesion,<sup>4</sup> and in a series of 38 sibships from south-east England, seven were discordant.<sup>5</sup> In view of these conflicting results, we studied affected sibs from the west of Scotland to determine whether there was concordance for the type of NTD.

## Methods

A register of all infants and fetuses affected by neural tube defect (NTD) who were delivered in the west of Scotland was compiled by one of us (HMM) during 1976 to 1986. Cases were ascertained from multiple sources including records of the regional paediatric surgical and pathology services, the records of a population based prenatal screening programme for NTD, and personal examination of labour room records from every maternity hospital in the region. From this register, sibships with more than one affected subject were identified. From an initial total of 88 sibships, three sibships with Meckel syndrome and 19 sibships with insufficient clinical and pathological information were excluded from further analysis.

Of 66 remaining sibships, 61 had two affected, four sibships had three affected, and one had four affected. None had consanguineous parents. The results of clinical and necropsy examinations were reviewed and the NTD was initially classified as either anencephaly (including anencephaly-spina bifida and occipital encephalocele) or spina bifida (open, closed, and occult spina bifida).

In 48 of these sibships (43 with two affected, four with three affected, and one with four affected) more exact classification of the type of NTD was possible on the basis of precise clinical, pathological, or radiological description of the lesion. In this series the results of necropsy were available in 102 cases (100%) and 50 cases also had radiological studies performed.

The classes of NTD which were distinguished are indicated in fig 1. In fig 2 we compare the frequencies of these various lesions in the familial series and a series of 197 consecutive, sporadic cases identified from NTD register entries made in 1980 to 1981. This classification scheme also permits *low* spina bifida (NTD sited below vertebral level T12) to be

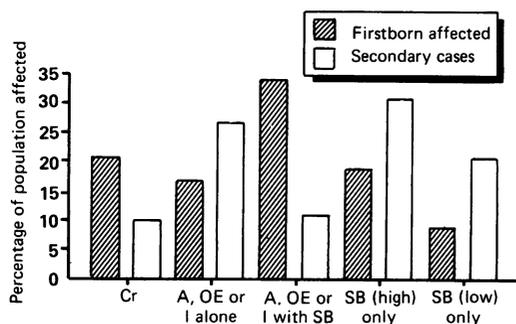


Figure 1 Note the differing heights of the hatched and white columns in each class of lesion. This indicates that the affected sib usually has a different lesion from the first born affected. Key to abbreviations used is given in the appendix.

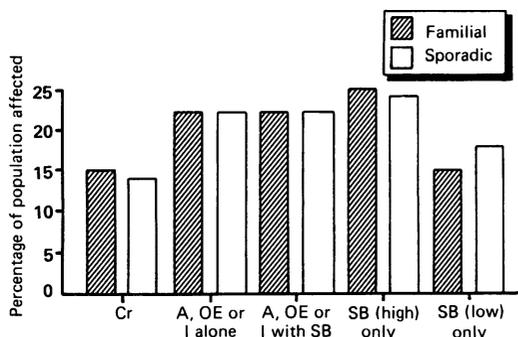


Figure 2 Close correspondence between proportions of the various classes of NTD in the familial and sporadically occurring series.

distinguished from *high* NTD (any lesion sited above T12 and possibly extending below this level).

## Results

### CLASSIFYING LESIONS AS EITHER ANENCEPHALY OR SPINA BIFIDA

The dataset comprises 66 pairs of first born and second born affected sibs. If the first born affected had anencephaly (47 cases), the second born was equally likely to have anencephaly (23 cases) or spina bifida (24 cases). Of 19 first born with spina bifida, 14 (74%) had a second born sib with the same defect. Thus, anencephaly did not breed true but there was a tendency for spina bifida to do so ( $\chi^2 = 4.263$ ,  $p < 0.05$ ).

### CLASSIFYING LESIONS ACCORDING TO THEIR LOCATION

In 48 sibships detailed in the appendix, the lesions were classified according to their location. A graphical representation is presented in fig 1 where the

first born affected ( $n = 48$ ) have been separated from secondary cases ( $n = 54$ ). If the second born had the same lesion as the first born, then similar numbers would be expected in each class, but this was not observed. In fig 2, the overall proportions of the different types of NTD in the familial cases is seen to be similar to the proportions of each type in the sporadically occurring series.

The male to female ratio was less than one in each category in fig 1, except in cases with a solitary lesion below T12, where a male preponderance was observed in both the familial (9M:6F) and sporadic series (20M:16F).

### CLASSIFYING THE NTD INTO HIGH AND LOW LESIONS

The ratios of *high:low* lesions were similar in the familial (87:15) and sporadic series (161:36) and the numbers of discordant (*high-low*) and concordant sibships were a good fit with those expected, given the frequencies of high and low lesions in the sporadic series ( $\chi^2 = 3.53$ ,  $p > 0.3$ ).

In the table, although numbers are small in some categories, there was no significant tendency for affected sibs to be concordant for the level of lesion (Fisher's exact test:  $p = 0.34$ ). It is noteworthy that the sibship with four affected by spina bifida comprised two males with *low* lesions and two females with *high* lesions. Of the four sibships with three affected, three comprised three cases with *high* lesions, while the fourth had two *high* lesions and one *low* lesion.

## Discussion

The suggestion that *low* spina bifida differs genetically from *high* spina bifida came from two North American studies which observed complete concordance for the level of lesion in a total of 25 sibships with two affected cases.<sup>23</sup> However, discordance for the level of lesion was present in four sibships from Newfoundland,<sup>4</sup> seven sibships from south-east England,<sup>5</sup> and, in this report, 14 sibships from the west of Scotland. In our study there was an excess of sibships concordant for *high* NTD (33 out of 48, 70%) which is comparable to the excess present in the study of Seller<sup>5</sup> (82%). In both our

Correspondence between lesions in first born affected and second born affected sibs after classifying lesions as either high or low NTD (total 48 affected sib pairs).

	Affected sib	
	High	Low
First born affected		
High	34	9
Low	5	0

( $p = 0.34$ , not significant).

series (familial and sporadic) and in the series of Seller,<sup>5</sup> there was an overall excess of *high* lesions (about 85%) and given this excess it is not surprising that we more frequently observed concordance between affected sibs for *high* NTD.

Our failure to confirm concordance in affected sibs for the level of NTD after classification of the lesion as *high* or *low* might be related to the mode of case ascertainment. The North American studies which showed concordance did not attempt complete ascertainment within a defined population, had no connection with a systematic prenatal screening programme, and had a preponderance of liveborn cases ascertained through spina bifida clinics. Not surprisingly, these cases mostly had *low* NTD. In contrast, the study from Newfoundland which reported discordant sibships was based on a larger epidemiological study of live and stillborn infants with NTD. Our study group was also less biased, being taken from a population based NTD register which was closely related to a prenatal screening programme for NTD. Thus, as mentioned above, we found a higher proportion of *high* NTD (85%), comparable to the proportion (87%) present in the study of Seller<sup>5</sup> from south-east England, which was also associated with a prenatal diagnosis programme. It is also interesting that we confirmed Seller's unexpected observation of a male preponderance in *low* spina bifida, which had prompted her to suggest that differing susceptibilities of male and female embryos to upper and lower NTD might be related to differences in their rate of early embryonic development.<sup>6</sup>

In previous UK data, there has been a tendency for sibs to have the same sort of NTD when cases are simply classified as either anencephaly or spina bifida.<sup>7</sup> North American data are conflicting on this point. A summary of published data in 1980 showed no tendency for anencephaly and spina bifida to breed true,<sup>7,9</sup> but more recent studies have shown a slight trend.<sup>2,3,8</sup> In our data there was a tendency for spina bifida to breed true although no such tendency existed for anencephaly.

An important practical issue is the suggestion, based on British Columbian data, that upper spina

bifida has a higher recurrence risk (7.8%) than lower spina bifida (0.7%).<sup>3</sup> Our study sheds no light on the recurrence risk in the west of Scotland, but it is interesting that previous data from this region indicated that the NTD recurrence risk, calculated from the number of positive amniocenteses after a previous NTD birth, fell slightly from 5.2% in 1975 to around 3% in 1983.<sup>10</sup> This slight decline was paralleled by a decline in the NTD rate from 5.2 per 1000 in 1979 to 2.4 per 1000 in 1985,<sup>11</sup> and it is consistent with the observed correlation between the recurrence rate and the local birth frequency. Moreover, the decline in the west of Scotland recurrence risk has occurred despite upper NTD being more frequent than lower NTD in this region. Since there is evidence from older studies that the sib risk is similar whether the proband has anencephaly or spina bifida,<sup>7</sup> we presently prefer to use in genetic counselling a single average recurrence risk of 4%, regardless of the level of lesion.

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## Appendix NTDs present in 48 sibships.

	1st born affected	2nd	3rd	4th	Summary
(1)	F SB(T/L)	M An			HH
(2)	F An	M Cr			HH
(3)	F An + SB(C/T)	F SB(T/L)			HH
(4)	F An + SB(C)	F SB(T/L)			HH
(5)	F OE	F E + SB(C/T/L/S)			HH
(6)	F SB(T/L)	M An + I + SB(C)			HH
(7)	M An	F SB(L)			HL
(8)	F An + SB(C/T)	F An + SB(C/T)			HH
(9)	F An + SB(C/T/L/S)	F An + SB(C)	M SB(L)		HHL
(10)	F SB(T/L)	M An + SB(C)	M An + SB(C)		HHH
(11)	F Cr	F I + SB(C/T)			HH
(12)	F Cr	F Cr			HH
(13)	M An + SB(C/T)	F An	F Cr		HHH
(14)	F An + SB(C/T)	M SB(L/S)			HL
(15)	F An	M An			HH
(16)	M SB(C)	F Cr			HH
(17)	F An	F An + SB(C)			HH
(18)	M An	M An + SB(C/T)			HH
(19)	F An	F SB(T/L/S)			HH
(20)	F An	M SB(L)			HL
(21)	F Cr	F SB(L/S)			HL
(22)	F Cr	M An + SB(C/T/L)			HH
(23)	F Cr	F SB(T/L)			HH
(24)	F SB(T/L)	F SB(L/S)			HL
(25)	M Cr	M An + SB(T/L/S)			HH
(26)	F Cr	M SB(T/L)			HH
(27)	F An	F An			HH
(28)	F An + SB(C/T)	F OE			HH
(29)	F SB(T/L)	M SB(T/L)			HH
(30)	M SB(S)	F SB(T/L)			LH
(31)	F SB(T)	F SB(L/S)			HL
(32)	M SB(L/S)	F SB(T/L)			LH
(33)	F An	F SB(T/L)			HH
(34)	F An	M An + SB(C/T)			HH
(35)	F Cr	F Cr			HH
(36)	M An	F SB(L/S)			HL
(37)	F An	M An + SB(C)			HH
(38)	F An	M SB(S)			HL
(39)	M Cr	F SB(T/L)			HH
(40)	M An	M SB(C)			HH
(41)	M SB(L/S)	F SB(T/L)			LH
(42)	M SB(T/L)	F SB(L/S)			HL
(43)	F Cr	F An + SB(C)			HH
(44)	M An	M An + SB(C)			HH
(45)	M SB(L)	F SB(T/L)			LH
(46)	M SB(L)	F SB(T)	F SB(T/L)	M SB(L/S)	LHHL
(47)	F SB(T/L)	F SB(T/L/S)			HH
(48)	M An + SB(C/T/L)	F An	M An		HHH

M = male, F = female, SB = spina bifida, C = cervical, T = thoracic, L = lumbar, S = sacral, An = anencephaly, Cr = craniorachischisis, OE = occipital encephalocele, E = encephalocele, I = iniencephaly, H = high, L = low.