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ORIGINAL ARTICLE

# Birth defects among maternal first cousins in Irish families with a neural tube defect

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**Abstract**
*Background* Maternal first cousins of an individual with a neural tube defect (NTD) are at increased risk for an NTD. It is not known if they are also at risk for other serious birth defects.
*Methods* We carried out an interview study of uncles and aunts and first cousins in Irish NTD families covering their pregnancy histories and the health of family members.
*Results* Maternal first cousins were more likely than paternal first cousins to have a birth defect (9.4% vs. 5.5%, $p = 0.02$; adjusted odds ratio: 1.72, 95% confidence interval: 1.04, 2.84).
*Conclusions* This study shows that two generations of distant relatives (uncles/aunts and first cousins) in NTD families have similar maternal excesses of NTDs and birth defects overall. Inheritance mechanisms favouring matrilineal transmission, currently unknown, may contribute to birth defect occurrence in these families.

**Keywords** Birth defects · Family studies · Irish · Matrilineal inheritance · Neural tube defects

## Introduction

Studies from North America and Europe of extended families where an individual has been born with a neural tube defect (NTD) provide evidence for matrilineal inheritance of NTDs, in that both maternal uncles and aunts and maternal first cousins have more NTDs than paternal relatives (for example, Chatkupt et al. [1]). Previously we showed that maternal uncles and aunts have more birth defects when all birth defects are considered [2]. This paper investigates the hypothesis that maternal first cousins have excess risks of birth defects overall.

## Methods

Families were identified through their participation in the local chapter of the Irish Association for Spina Bifida and Hydrocephalus and through word of mouth. Probands were liveborn or stillborn and affected with any one of four types of NTD—anencephaly, spina bifida, spina bifida occulta or encephalocele. The original nuclear families were interviewed between 1995 and 2002; uncles and aunts were interviewed between 2000 and 2002; first cousins were interviewed between April, 2002 and November, 2004. The family history sought similar information, including reproductive history, the health of each respondent and their children, including birth defects, medical conditions and cancer [2].

The participating nuclear families reported 534 living uncles and aunts, of whom 373 were interviewed. The uncles and aunts identified 1,121 pregnancies born to them ("first cousin pregnancies"). This number included 124 miscarriages which were deleted from this analysis, leaving 997 first cousin pregnancies. Of these, 669 were alive,

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older than 17 years of age, not mentally incapacitated or confined to an institution and thus, eligible for interview; 431 were successfully interviewed. Reasons for non-interview included refusal by the uncle or aunt to allow contact ($N = 95$), first cousin refusal ($N = 29$), not located ($N = 113$). The refusal rate by first cousins was 6.3% (29/29 + 431). This report is based on information obtained by interview with uncles and aunts and from first cousins. Birth defects were accepted as reported either by the uncles and aunts or by the first cousins at interview. Potential biases were evaluated in the analysis.

The Dublin component of the European Union's EUROCAT registry of congenital anomalies (www.eurocat.ulster.ac.uk) served as the comparison group for individual birth defects. Due to potential problems with the different methods of ascertainment between EUROCAT and this study, no overall comparisons are presented.

Some birth defects were excluded including minor defects, such as heart murmur, hip click, isolated dislocated hip and birth mark. Others were excluded from the analysis since they were single gene defects or other types of anomalies, including haemochromatosis, Down syndrome, cystic fibrosis, propionic acidemia, tuberous sclerosis and mental retardation. Birth defects included any neural tube defect, including those that are considered clinically related, such as dimple at base of spine. For the purpose of this report, birth defects reported by relatives, such as 'hole in the heart' and 'congenital heart disease' were classified as ventricular septal defects. In addition, the term "birth defects overall" was used to denote the totality of all birth defects that is the outcome of this study.

### Statistical analyses

Statistical analyses were carried out with SAS version 8.2 (Statistical Analysis System, Cary, North Carolina). Simple comparisons were tested for statistical significance with chi-square tests with $\alpha = 0.05$, and two-tailed tests. Stratified analyses were done to investigate the possibility of heterogeneity in the relationship between line and birth defects. By controlling for potential confounding the logistic regression models evaluated the independent contribution of line to the occurrence of birth defects. Continuous variables were dichotomized for modelling purposes.

## Results

Birth defects were present in 74 or 7.4%, out of the 997 first cousins of the proband. There were no significant differences in the proportion of first cousins with birth defects according to the type of NTD of the proband, or the proband's year of birth; female probands were more likely to have first cousins with birth defects than male probands ($p = 0.03$). There were no differences in the proportion of cousins with birth defects according to the age of the related uncle or aunt or their gender, or mother's smoking and drinking habits. Maternal first cousins were more likely to have birth defects than paternal first cousins ($p = 0.02$). Uncles and aunts born more recently were more likely to have offspring (first cousins) with birth defects ($p = 0.002$). Folic acid taken either before or during pregnancy was positively related to the occurrence of a birth defect in the first cousins ($p = 0.003$). Since these last two relationships were unexpected, they are explored further below. No characteristic of first cousins was significantly associated with an increase in birth defects (Table 1).

Birth defects were more likely in more recent years in all three groups of relatives (Table 1). The possibility that recall bias could be the explanation was evaluated by looking at whether the birth defect was reported by the first cousin at interview (self-report), or reported by the uncle/aunt (the parent). For all three time periods birth defects reported by uncles/aunts were more frequent in the most recent period. In contrast, self-reports showed little or no difference in occurrence of birth defects by either earlier or late interval of year of birth (data not shown). Thus, the data support the explanation of recall bias with better recall in more recent years.

The apparent association of folic acid intake with birth defects may also be explained by reporting bias. When the analysis was restricted to aunts reporting on their own most recent pregnancies (1995–2000) there were no significant associations between folic acid and birth defects either when folic acid was taken before pregnancy or during early pregnancy (21.0 vs. 11.1%, $p = 0.72$ and 10.7 vs. 33.3%, $p = 0.28$, respectively), suggesting that the association is spurious.

Table 2 shows the frequencies of birth defects overall and the frequencies of NTDs according to line (paternal versus maternal), gender of parent (uncle/aunt) and gender of first cousin. For birth defects overall, female first cousins born to maternal aunts had the highest percentage of birth defects at 13.5%; comparing this to the percentage with birth defects of all other cousins gave a significant odds ratio of 2.24 (95% CI: 1.24, 4.03). The rate of NTDs among maternal versus paternal first cousins was 2.59 times greater, but this odds ratio did not reach statistical significance (95% CI: 0.45, 19.32), probably due to small number of events.

In a logistic regression model that included main effect terms for line, gender of proband, uncle/aunt and first cousin, year of birth of first cousin, a term for open spina bifida versus other type of NTD, folic acid use before and during early pregnancy, and whether the first cousin was

**Table 1** Birth defects among first cousins of probands with NTDs, according to characteristics of the proband, uncles/aunts and first cousins themselves

| | First cousins with birth defects | | |
|---|---|---|---|
| | *N* | % | *p* |
| Overall | 74/997 | 7.4 | – |
| *Characteristics of proband* | | | |
| Proband's NTD diagnosis | | | |
| Anencephaly | 5/57 | 8.8 | 0.34 |
| Spina bifida occulta | 8/79 | 10.1 | |
| Open spina bifida | 60/838 | 7.2 | |
| Encephalocele | 1/23 | 4.4 | |
| Proband's gender | | | |
| Male | 32/552 | 5.8 | 0.03 |
| Female | 42/445 | 9.4 | |
| Proband's year of birth | | | |
| 1957–1977 | 31/486 | 6.4 | 0.22 |
| 1978–1995 | 43/511 | 8.4 | |
| *Characteristics of uncles/aunts* | | | |
| Related parent's age at FC birth | | | |
| 18–29 | 41/466 | 8.8 | 0.12 |
| 30–50 | 32/517 | 6.2 | |
| Gender of related uncle/aunt | | | |
| Male | 34/437 | 7.8 | 0.70 |
| Female | 40/560 | 7.1 | |
| Year of birth of related uncle/aunt | | | |
| 1916–1948 | 25/506 | 4.9 | 0.002 |
| 1949–1971 | 49/491 | 10.0 | |
| Folic acid tablets taken on their own *before* pregnancy | | | |
| Yes | 10/60 | 16.7 | 0.005 |
| No | 63/922 | 6.8 | |
| Folic acid tablets taken on their own *during* pregnancy | | | |
| Yes | 19/139 | 13.7 | 0.003 |
| No | 55/838 | 6.6 | |
| Did (U&A) mother smoke *before* FC pregnancy | | | |
| Yes | 22/259 | 8.5 | 0.47 |
| No | 52/730 | 7.1 | |
| Did (U&A) mother smoke *during* FC pregnancy | | | |
| Yes | 18/195 | 7.0 | 0.30 |
| No | 56/796 | 9.2 | |
| Line | | | |
| Paternal line | 28/506 | 5.5 | 0.02 |
| Maternal line | 46/491 | 9.4 | |
| *Characteristics of first cousins* | | | |
| Gender of first cousin | | | |
| Male | 34/482 | 7.1 | 0.61 |
| Female | 40/506 | 7.9 | |
| Year of birth | | | |
| 1946–1978 | 33/503 | 6.6 | 0.30 |
| 1979–2000 | 41/494 | 8.3 | |
| Birth order | | | |
| 1–3 | 46/526 | 8.8 | 0.09 |
| 4–10 | 28/471 | 5.9 | |
| Family size | | | |
| 1–3 | 41/521 | 7.9 | 0.57 |
| 4–10 | 33/476 | 6.9 | |
| Was first cousin interviewed? | | | |
| Yes | 28/431 | 6.5 | 0.33 |
| No | 46/566 | 8.1 | |

Abbreviations: *U&A* uncle/aunt, *FC* first cousin

interviewed or not, the effect of maternal line remained statistically significant, with an odds ratio of 1.72 (95% CI: 1.04, 2.84, $p = 0.04$).

The occurrence of individual birth defects by line was evaluated; no difference achieved statistical significance (Supplementary Table 1). Overall, the percentage of open spina bifida among first cousins was 7 per 1,000; among maternal cousins the percentage rose to 1% (1.02%). Out of the 24 types of defects examined, 17 occurred more often among maternal cousins, 4 occurred more frequently among paternal cousins and 3 occurred equally often in both groups. None of the seven pregnancies that ended in spina bifida was supplemented with folic acid before pregnancy and only one was supplemented during gestation.

The matrilineal excess in first cousins was not consistent across types of NTD in the proband (Supplementary Table 2): the two largest NTD groups in terms of number of first cousins—open spina bifida and spina bifida occulta—showed a clear matrilineal effect, while the two smaller groups—anencephaly and encephalocele—had no affected maternal first cousins. This variability could be due to the small number of families. Concordance for type of NTD between probands and first cousins also varied. Of the eight first cousins with NTDs, the single spina bifida occulta occurred in a family where the proband had open spina bifida. Of the remaining seven cousins with open spina bifida, five were related to probands with open spina bifida, one to an anencephalic and one to a proband with spina bifida occulta.

Comparing the prevalence of individual birth defects among first cousins overall with corresponding entities from the Dublin EUROCAT registry showed that open spina bifida occurred 3.67 times more frequently among first cousins (unadjusted odds ratio (uOR) = 3.67, 95% CI: 1.60, 7.66, $p < 0.001$). Ventricular septal defects occurred twice as often, but the difference was not statistically significant (uOR = 2.31, 95% CI: 0.85, 5.76, $p = 0.11$).

**Table 2** First cousins of NTD probands with birth defects according to the line (paternal/maternal) of the first cousin, the gender of the uncle/aunt and of the first cousin

| | No. with birth defects[a] | | No. with neural tube defects (anencephaly and open spina bifida) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Paternal uncles' male children | 8/103 | 7.8 | 2 | 1.94 |
| Paternal uncles' female children | 10/126 | 7.9 | 0 | – |
| Paternal aunts' male children | 4/130 | 3.0 | 0 | – |
| Paternal aunts' female children | 6/140 | 4.3 | 0 | – |
| Maternal uncles' male children | 11/104 | 10.6 | 2 | 1.92 |
| Maternal uncles' female children | 5/99 | 5.1 | 0 | – |
| Maternal aunts' male children | 11/141 | 7.8 | 1 | 0.70 |
| Maternal aunts' female children | 19/141 | 13.5[b] | 2 | 1.42 |

[a] Gender missing for 13 first cousins

[b] Comparing maternal aunts' female children with birth defects to all other groups of relatives, 13.5% vs. 6.5%, $p = 0.006$; odds ratio: 2.24, 95% CI: 1.24, 4.03

The NTD results from the present study were added to results from 9 other family studies [1, 3–10] that evaluated the percentage of NTDs among first cousins by gender and type of relationship (Supplementary Table 3). While the percentage of affected cousins varied, and methods of ascertainment were different, in all studies more NTDs occurred among maternal than paternal first cousins. One study [11], which did not find a maternal excess, is not included since the raw data was not provided. The total NTD prevalence of 0.46% for paternal first cousins compared to a prevalence of 1.01% for maternal first cousins provides an odds ratio of 2.20 (95% CI: 1.63, 2.97, $p < 0.0001$). In order to determine if the excess was from the female line, two further comparisons were performed. First, the percentage of NTDs occurring in first cousins of both sexes born to maternal aunts was compared to that in all other first cousins combined and yielded a statistically significant odds ratio of 2.69 (95% CI 2.02, 3.57). Second, the percentage of NTDs occurring in female first cousins born to maternal aunts was compared with all other first cousins combined and showed a similar statistically significant excess with an odds ratio of 2.46 (95% CI: 1.42, 4.22). In addition to the present study, only three other studies provided the gender of first cousins [1, 5, 8].

Results from our previous report on matrilineal patterns among uncles and aunts in these same families [2] were united with results from first cousins in a graphic representation of the maternal excesses of both NTDs and birth defects overall in two consecutive generations (Fig. 1). The patterns across generations were very similar and the odds ratios did not diminish markedly with increasing genetic distance from the proband.

## Discussion

This study confirmed the initial hypothesis, finding that maternal first cousins in Irish families with NTDs had more birth defects than paternal first cousins, with an odds ratio of 1.72 (95% CI: 1.04, 2.84, $p = 0.04$). Further, there were significantly higher rates of birth defects among female first cousins born to maternal aunts. This study joins a previous report of birth defects among uncles and aunts in these same families and shows that an excess of matrilineal birth defects persisted through at least two generations [2]. Within overall birth defects, the study looked at the patterns of recurrence of NTDs within these families and also as part of a meta-analysis combining previous studies. All 9 previous studies, and this study, agree that maternal first cousins are more likely than paternal first cousins to have NTDs, with female first cousins born to maternal aunts being significantly more at risk than other types of first cousins. Matrilineal patterns among first cousins of both NTDs and birth defects overall are similar to those previously reported among uncles and aunts in these families. These studies support the hypothesis that the underlying susceptibility leading to NTDs can result in other forms of abnormal development.

No other study has been found that reported on occurrence of other birth defects in first cousins. Reports of other birth defects in probands and in siblings refer to congenital heart defects, kidney anomalies and facial clefts [12]. Hunter [9] speculated that the associated malformations tended to be of the schisis type, that is, defects involving a midline developmental field [13]. Our studies found that congenital heart defects occurred to excess over population-based rates among both uncles and aunts and among first cousins.

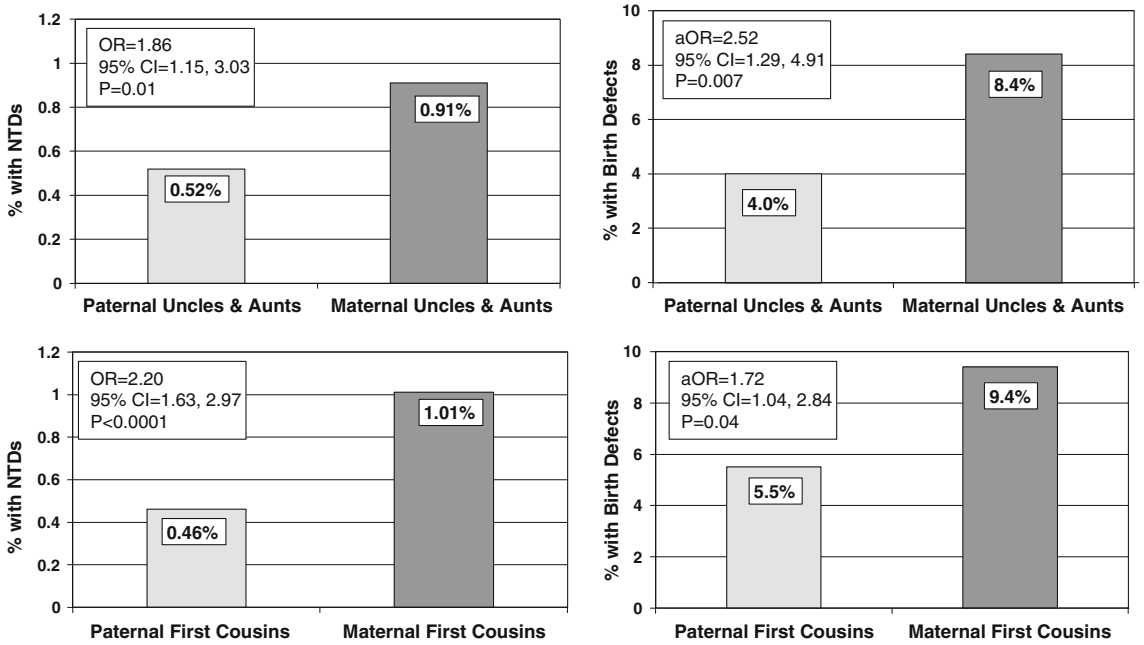


**Fig. 1** Relatives with NTDs and with birth defects overall (%) comparing maternal versus paternal relatives, among uncles and aunts and among first cousins in Irish families with neural tube defects (*OR* odds ratio, *aOR* adjusted odds ratio, *CI* 95% confidence interval)

Possible explanations for the maternal excess could implicate environmental as well as genetic factors. Maternal conditions, such as diabetes, have been linked to NTDs [14], but none of the mothers of first cousins with birth defects in this study had diabetes. No mother was taking anti-epileptic drugs. A genetic mechanism seems a more likely explanation for these observations. The evidence presented concerning multi-generational patterns of birth defects in uncles and aunts and in first cousins suggests a number of possible genetic mechanisms. Available evidence indicates that maternal genes can be involved more often than embryonic genes in production of an NTD [15]. Mitochondrial inheritance, in which traits are passed on from mother to daughter through mitochondrial DNA, is a possibility that remains to be explored in the context of familial cases of NTDs. Genomic imprinting, where the phenotype depends on whether the gene is transmitted through the mother or the father has also been proposed to explain these observations [16]). Recently, imprinting and methylation have been included among a variety of epigenetic mechanisms that could explain the stability of characteristics through cell division without changes to the underlying DNA [17].

While there is evidence of biased reporting in these data, the strength of this study lies in compiling reported birth defects from parents and from the affected individuals themselves, so that these biases can be evaluated. The biases detected do not impact on the main findings.

This paper has shown that birth defects of all types considered together occur more frequently among maternal than among paternal first cousins of NTD probands, and are most frequent among daughters of maternal aunts. Birth defects have many different causes; the opportunity may exist to reduce the impact from at least one source by encouraging increased intake of folic acid.

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## References

1. Chatkupt S, Jaggi M, Mitruka BS et al (1994) Study of genetics, epidemiology and vitamin usage in familial spina bifida in the United States in the 1990s. Neurol 44:65–70
2. Byrne J (2008) Birth defects in uncles and aunts from Irish families with neural tube defects. Birth Defects Res A Clin Mol Teratol 82(1):8–15
3. Williamson E (1965) Incidence and family aggregation of major congenital malformations of the central nervous system. J Med Genet 2:161–172
4. Carter CO, David PA, Laurence KM (1968) A family study of major central nervous system malformations in South Wales. J Med Genet 5:81–93
5. Carter CO, Evans K (1973) Spina bifida and anencephalus in greater London. J Med Genet 10(3):209–234

6. Zackai EH, Spielman RS, Mellman WJ et al (1978) The risk of neural tube defects to first cousins of affected individuals. UCLA Forum Med Sci 20:99–102
7. Lippman-Hand A, Fraser FC, Biddle CJ (1978) Indications for prenatal diagnosis in relatives of patients with neural tube defects. Obstet Gynecol 51(1):72–76
8. Nevin NC, Johnston WP (1980) A family study of spina bifida and anencephalus in Belfast, Northern Ireland (1964 to 1968). J Med Genet 17(3):203–211
9. Hunter AGW (1984) Neural tube defects in Eastern Ontario and Western Quebec: demography and family data. Am J Med Genet 19(1):45–63
10. McManus S (1987) Neural tube defects: identification of 'high risk' women. Ir Med J 80(6):166–168
11. Toriello HV, Higgins JV (1983) Occurrence of neural tube defects among first-, second-, and third-degree relatives of probands: results of a United States study. Am J Med Genet 15(4):601–606
12. Khoury MJ, Erickson JD, James LD (1982) Etiologic heterogeneity of neural tube defects. II. Clues from family studies. Am J Hum Genet 34(6):980–987
13. Opitz JM, Gilbert EW (1982) CNS anomalies and the midline as a "developmental field". Am J Med Genet 12(4):443–455
14. Macintosh MC, Fleming KM, Bailey JA et al (2006) Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 333(7560):177
15. Doolin MT, Barbaux S, McDonnell M et al (2002) Maternal genetic effects, exerted by genes involved in homocysteine remethylation, influence the risk of spina bifida. Am J Hum Genet 71(5):1222–1226
16. Chatkupt S, Lucek PR, Koenigsberger MR et al (1992) Parental sex effect in spina bifida: a role for genomic imprinting? Am J Med Genet 44(4):508–512
17. Whitelaw E (2006) Epigenetics: sins of the fathers, and their fathers. Eur J Hum Genet 14(2):131–132