

Three generations of matrilineal excess of birth defects in Irish families with neural tube defects

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Abstract

Background Neural tube defects (NTDs) and birth defects overall are more likely to occur among maternal compared to paternal relatives in two generations (uncles/aunts and first cousins) of Irish families where an individual has been born with an NTD.

Aims The aim of this study was to determine if the matrilineal excess persisted into the third generation.

Methods First cousins were interviewed about their pregnancy outcomes and their offsprings' health.

Results Maternal first cousins once removed (FCOR) were more likely to have birth defects than paternal FCOR: 6.7 versus 3.5% (adjusted odds ratio 1.49, 95% CI 0.57, 3.89). No NTDs occurred. Folic acid supplementation significantly reduced the risk of birth defects ($P = 0.04$).

Conclusions This study demonstrates an excess of birth defects among maternal relatives in three consecutive generations of NTD families, and supports the hypothesis that an underlying mechanism links distant maternal relatives in at least some NTD families.

Keywords Neural tube defects · Family studies · Birth defects · Irish · Matrilineal effects

Introduction

In families where an NTD has occurred maternal, compared to paternal, relatives in at least two successive

generations are at excess risk of neural tube defects (NTDs) [1–3]. NTDs are characterized by heterogeneity of type. For instance, recurrences within families are often of different NTD types, other malformations occur to excess among probands, NTDs occur more often in sibs of children with other malformations, families with congenital scoliosis are at increased risk for NTDs, and relatives of infants with spina bifida are more likely to have spina bifida occulta [4–8]. It is possible that this heterogeneity includes excess occurrences of other types of birth defects in distant relatives. We have earlier shown excess rates of birth defects overall among maternal relatives (uncles/aunts and first cousins) in two consecutive generations of Irish families with NTDs [1, 2]. The question to be evaluated here was: does this matrilineal effect continue into the third generation, i.e., do maternal compared to paternal first cousins once removed in Irish families with NTDs have excess rates of birth defects?

Methods

This study reports results from Phase III studies of Irish NTD families by the Boyne Research Institute (BRI). Phase I evaluated pregnancy histories and the health of siblings in the original nuclear families. These families were identified through their membership in the Louth–Meath branch of the Irish Association for Spina Bifida and Hydrocephalus, and the Ballymena branch of the (UK) Association for Spina Bifida and Hydrocephalus. Families were also recruited through word of mouth and through media in the Louth–Meath area. Phase II subjects (uncles and aunts) were identified by their siblings during Phase I. At interview uncles and aunts provided information on their pregnancies and the health of their offspring (the first

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cousins). Phase III consisted of interviews with first cousins. To the data from the original study of first cousins (Phase III) were added pregnancies ascertained during a follow-up study of all individuals known to us who were in their reproductive years (interviews from 2007 to 2009). The follow-up study identified a further 67 new pregnancies, which were added to the original study data for analysis. The original study included pregnancies to first cousins from 33 families; the follow-up study included pregnancies from 23 families, of whom all except two families had participated in the original study. There was no significant difference in the rates of birth defects between the follow-up study and the original study (5.08 vs. 6.04%, $P = 0.77$). We report here on the birth defect status of the children of the first cousins who are the first cousins once removed (FCOR). Details of this study have been published previously [9].

First cousins were interviewed initially between 2002 and 2004. Eligible relatives were interviewed again (and some for the first time) as part of the follow-up study in 2008–2009. Pregnancies were excluded if they ended in fetal loss, or a twin pregnancy, or current pregnancies, yielding a total of 424 singleton liveborn children. Birth defects that were excluded comprised minor defects (heart murmurs, moles and birth marks), chromosome anomalies, cerebral palsy and single gene conditions. Results relating to miscarriage are reported in a separate publication [10]. For each pregnancy separately respondents were asked a set of questions relating to the 3 months before the pregnancy started, and to the first 3 months of each pregnancy. Besides a special diet, or drugs, smoking, alcohol and

medications, respondents were asked if they took multivitamins with or without folic acid or folic acid supplements on their own. In addition, questions were asked about German measles, a heavy cold, herpes, toxoplasma and diabetes or other illnesses during pregnancy. The dose of the folic acid supplements was not asked. From previous studies we know that most women were taking the 400 μg dose (“Clonfolic”) commonly available over the counter in Ireland.

The Ethics Board of the Boyne Research Institute approved this study. Statistical analyses were carried out with SAS (Statistical Analysis System, Cary, NC, v9.1). Simple comparisons were tested for statistical significance with Chi-square tests with $\alpha = 0.05$, and two-tailed tests. Logistic regression models and stratified analysis controlled for potential confounding. Effect modification was assessed by means of the Breslow-Day statistic. Folic acid supplementation was categorized into fully (folic acid tablets on their own taken both before and during early pregnancy), partial (during pregnancy, not before), or not supplemented (not taken at either time).

Results

The overall proportion of FCOR with birth defects was 5.2% (22/424). When evaluated according to the gender of each linking relative, the percentage of maternal first cousins with birth defects was consistently greater than the percentage of paternal first cousins (Fig. 1). The rate of birth defects did not vary according to the following

Fig. 1 Percent of first cousins once removed with birth defects by line and gender. For example, the first bar reads “3.7% of first cousins once removed born to male first cousins, who were born to male uncles/aunts on the paternal side, had birth defects”. UA uncles/aunts, FC first cousins, FCOR first cousins once removed

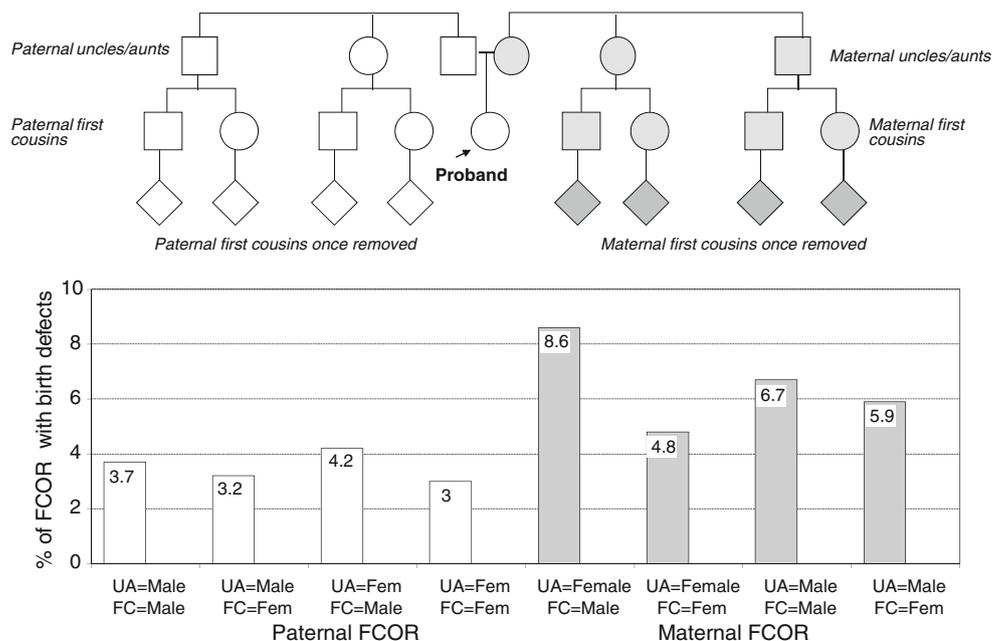


Table 1 First cousins once removed (FCOR) with birth defects by group and by maternal versus paternal line

FCOR with birth defects by group	Paternal FCOR (<i>N</i>)	Maternal FCOR (<i>N</i>)	Total (<i>N</i>)
Cardiac defects	1	4	5
Craniofacial defects	2	3	5
Dimple/pinhole at base of spine	2	3	5
Genitourinary anomalies	2	1	3
Limb defects	0	3	3
Endocrine defects	0	1	1
Total	7	15	22

characteristics: proband's NTD diagnosis, first cousins' age at birth of FCOR, gender of related first cousins or of FCOR, year of birth of FCOR, family size or birth order, birth defects in first cousins, outcome of FCOR pregnancy (term vs. preterm), multivitamins with or without folic acid taken before or during pregnancy, smoking or drinking before or during pregnancy (data not shown). Folic acid supplementation was associated with a significant protective trend ($P = 0.04$): the proportion of pregnancies ending in a child with a birth defect was 3.5% if pregnancies were fully supplemented, 4.6% for partial supplementation and 8.2% for no supplementation. First cousins interviewed alone reported fewer FCOR with birth defects than those interviewed in the company of the other parent ($P = 0.03$). Maternal FCOR were more likely to be born with birth defects than paternal FCOR (6.7 vs. 3.5%, $P = 0.14$), with an unadjusted odds ratio of 1.98 and 95% confidence interval (CI) of 0.79–5.00.

A number of characteristics were evaluated in a stratified analysis to determine if the maternal excess varied by levels of each characteristic. No characteristic, including those listed above, affected the adjusted (Mantel–Haenszel) odds ratio, which varied from 1.77 to 2.77. A logistic regression analysis was carried out to determine if the odds ratio describing the association between maternal relatives and birth defects was affected by inclusion of potential confounders. In a model that included terms for open spina bifida versus other types of NTDs, type of respondent, and folic acid taken during early pregnancy, the adjusted odds ratio for maternal line was 1.49 (95% CI 0.57, 3.89).

Table 1 shows the individual categories of birth defects present in FCOR overall, and according to paternal or maternal line. No FCOR was reported to have a NTD. Among the birth defects were dimple at the base of the spine ($N = 5$), congenital heart disease ($N = 3$) fatal in all cases, foot deformity ($N = 3$), cleft lip/palate ($N = 1$), cryptorchidism ($N = 1$) and hypospadias ($N = 1$). Fifteen maternal FCOR had birth defects compared to seven paternal FCOR. Seven categories of birth defect occurred more frequently among maternal relatives compared to only two categories among paternal relatives.

Discussion

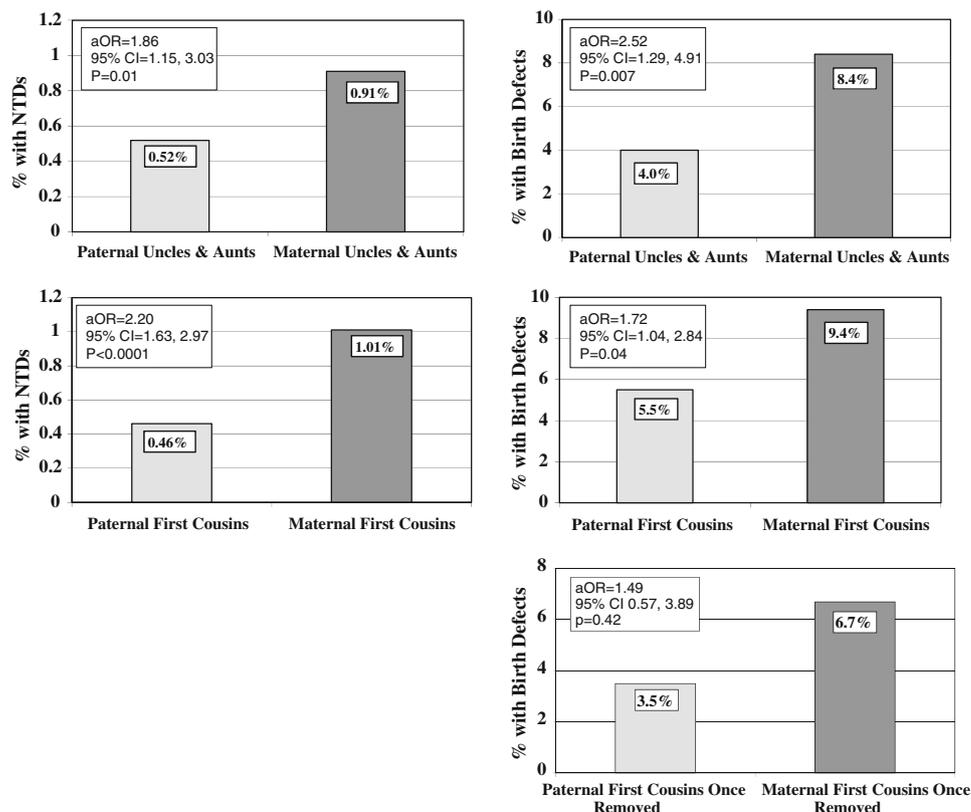
Our studies show for the first time that in three consecutive generations of Irish families with NTDs, uncles/aunts, first cousins and now, first cousins once removed, maternal relatives had more birth defects overall than paternal relatives, with about a twofold excess risk (Fig. 2). Although no NTDs occurred among FCOR, the pattern of maternal excess for both NTDs and for birth defects overall is strikingly similar among uncles/aunts, among first cousins and now among first cousins once removed. Besides the present study, no study has been found concerning birth defects overall among FCOR. Considering NTDs alone, there is persuasive evidence for a maternal excess; older reports are summarized in earlier publications from this study [1–2]. Two of these older studies reported significantly more NTDs in maternal versus paternal 'second cousins', presumably the offspring of first cousins, or FCOR [11–12]. Recently, Deak et al. [3] reported more than twice as many NTDs among maternal versus paternal relatives.

No NTDs were reported among FCOR. This may be due to the relatively high percentage (62%) of first cousins taking folic acid during early pregnancy. It is also true that over the last 60 years the rate of NTDs in Ireland has fallen dramatically [13] for reasons that are not clear, but may be related to improved diet.

In these three reports from Irish families, we make the argument by analogy that the excess of birth defects overall behaves in a similar way to the excess of NTDs. There may be a common mechanism linking the two. Supportive evidence comes from one report of excess rates of NTDs in sibs of children with other malformations [6], and a study of recurrent rearrangements in chromosome 1 showing a variety of clinical manifestations in individuals with the same microdeletion [14].

Taken together, these three reports concerning relatives in Irish families with NTDs document an excess of NTDs and of birth defects overall among maternal relatives. The risk does not seem to diminish with genetic distance from the proband. Prepregnancy counseling should allude to the risks that maternal relatives, even distant maternal

Fig. 2 The risk of neural tube defects and of birth defects overall among three generations in Irish families with neural tube defects (redrawn from Byrne [1, 2]). *aOR* adjusted odds ratio, *CI* confidence interval



relatives, have of a pregnancy with a birth defect and the beneficial effects of folic acid. Our data relate only to the 400 µg folic acid dose. There may be some justification for a randomized controlled trial of different doses of folic acid to determine their efficacy.

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