Familial cancer and developmental dyslexia: an observational pilot study

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The aim of the study was to test the hypothesis that raised platelet-activating factor (PAF) may contribute to the aetiology of developmental dyslexia. PAF is a potent proinflammatory mediator which signals cell damage and facilitates natural killer cell activity. Raised PAF may help protect against tumourigenesis. As dyslexia has a partial genetic basis, the PAF hypothesis predicts that dyslexia may be negatively associated with a family history of cancer. To test this prediction, children with dyslexia (n=163) and children without dyslexia (n=154), with (n=152) and without (n=165) a family history of cancer (total n=317; mean age 11 years 5 months, SD 2 years 11 months), were compared on standard psychometrics (British Ability Scales subtests). Results showed that proportionately fewer children with dyslexia (38%) than controls (58.4%) had a family history of cancer, and there was some evidence of a 'dose' effect: children who had more relatives with cancer showed better reading and spelling. It was concluded that children at genetic risk of dyslexia who have a family history of cancer have better reading and spelling than those without a family history of cancer, confirming the prediction of the PAF hypothesis.

See last page for list of abbreviations.

Developmental dyslexia is a neurodevelopmental learning disability characterized by both structural (Galaburda 1993) and functional (Eden et al. 1996) brain differences and estimated to affect 5–10% of UK children (Turner 1997). It involves unexpectedly poor reading relative to general intelligence, not explained by other factors, such as socioeconomic background or gross neurological deficit. Dyslexia has a considerable genetic component (Castles et al. 1999, Gayan and Olson 1999, Kaplan et al. 2002), but the mechanisms that give rise to the condition remain unclear.

It has been proposed that levels of proinflammatory mediators such as platelet-activating factor (PAF) may be raised in dyslexia (Taylor et al. 2001). This hypothesis makes radical predictions about relationships between dyslexia and common clinical conditions. One example is high blood pressure: PAF is a potent hypotensive agent, so people with dyslexia and their families should be less likely to suffer from high blood pressure (Taylor et al. 2001). This prediction, unlikely to have been made by any other theory of dyslexia, has recently been confirmed at the familial level (Taylor and Stein 2002).

PAF plays an early and important facilitating role in the body's immune responses, stimulating cytokine production and acting as a sensor of cell damage (Walterscheid et al. 2002). Conditions in which the immune system is deficient (e.g. AIDS) are associated with a higher risk of some cancers especially, though not exclusively, Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical carcinoma (Smith et al. 1998). If enhanced immune function is associated with lower risk of cancer, individuals with higher PAF levels may be less likely to develop tumours.

In neurons PAF is pro-apoptotic in vitro and in vivo (Bennett et al. 1998, Ogden et al. 1998). Its role in cell death and tumourigenesis elsewhere in the body remains unclear, and may differ according to cancer type and kind of study. Some studies suggest that PAF may promote tumour cell migration and angiogenesis (Bussolati et al. 2000), i.e. that it may favour the development of established tumours. However, PAF has also been observed to inhibit cancer invasion (Kotelevets et al. 1998, Noe et al. 1999). Moreover, PAF and its receptor are thought to be crucially involved in the tumour-killing activity of resting human natural killer cells (Berthou et al. 2000). A comparison of healthy and tumour tissue in patients with lung cancer found lower levels of PAF in tumour tissue, due to elevated activity of its metabolizing enzyme PAF acetylhydrolase (Denizot et al. 2001). It seems at least possible, therefore, that raised PAF levels could decrease the risk of developing cancer (although established tumours might be faster-growing and more likely to undergo metastasis (Im et al. 1996).

When investigating the comorbidity of psychiatric diseases such as schizophrenia with other medical conditions, the usual method is to match individuals from extremely large databases of psychiatric and medical records. Dyslexia, however, is neither a psychiatric disorder nor a notifiable medical condition. The dataset used here, despite being one of the largest datasets of dyslexic children available, does not have anywhere near the numbers required to test conclusively for an association between cancer and dyslexia in children. Nor was it possible to investigate specific disease types, although 'cancer' of course is aetiologically heterogeneous, involving varying numbers of inherited and environmentally-induced mutations in a range of proto-oncogenes and tumour suppressor genes.

This study uses a case-control approach instead, with data from a set of children with and without dyslexia from families in which at least one child was thought to have reading problems. Information was analyzed about the family medical history of children with and without dyslexia participating in research into the genetics of reading disability (Fisher et al. 1999, 2002). If genetic (or other) factors contribute to raised PAF levels in dyslexia, any protective effect of such factors against cancer should be seen in the families of people with dyslexia as well as in dyslexic individuals themselves. It is worth noting that analysis at this familial level, together with the aetiological heterogeneity inherent in the term 'cancer' should mediate against finding statistically significant results in this pilot study.

Method

The dataset (n=317) comprised a sample of 163 children with dyslexia and 154 children without dyslexia from 202 families in which at least one child was thought to have reading problems. Families were recruited from a research clinic for children with reading problems at the Royal Berkshire Hospital, Reading, UK. Patients were referred to the clinic by their general practitioner or other medical professional and were screened for gross neurological, visual, and auditory problems before being classified as having dyslexia (or not; i.e. control children were either referred to the clinic but not classified as dyslexic [87%] or were siblings of children who were referred to the clinic and classified as dyslexic [13%]). Study families completed questionnaires about their medical history. Specifically, they were asked if any member of the family had suffered from cancer, insulin-dependent diabetes or non-insulin-dependent diabetes. Diabetes was chosen for comparison because, like cancer, the aetiology is complex and variable, with both environmental and genetic components contributing. Responses to the questionnaires were used to classify individual participants as having a family history of cancer (C+) or having no family history of cancer (C–); and as having a family history of diabetes (D+) or having no family history of diabetes (D–). Table I shows the numbers in each group.

Table I: Participant groups identified in the study

Participant group	*Dyslexic n=163*	*Control n=154*	*Total n=317 (%)*
Males	107	73	180 (56.8)
Females	56	81	137 (43.2)
C+	62	90	152 (47.9)
C–	101	64	165 (52.1)
D+ (IDDM)	14	21	35 (11)
D– (IDDM)	149	133	282 (89)
D+ (NIDDM)	27	24	51 (16.1)
D– (NIDDM)	136	130	266 (83.9)
D+ (TOTAL)	36	40	76 (24)
D– (TOTAL)	127	114	241 (76)

C+, participants with a family history of cancer; C–, no family history of cancer; D+, family history of diabetes; D–, no family history of diabetes; IDDM, insulin-dependent diabetes; NIDDM, non-insulin-dependent diabetes.

STATISTICAL POWER

This is a pilot study with predetermined sample sizes of 152 participants with a family history of cancer, and 165 participants without a family history of cancer. A power level of 80% was used (i.e. β=0.2), with α set at 0.01, as a Type II error (failing to detect an existing relationship) was considered less problematic than a Type I error ('detecting' a non-existing relationship). The proportion of participants with a family history of cancer who were classed as having dyslexia was 62/152=0.41, while the proportion of participants who did not have a family history of cancer and were classed as dyslexic was 101/165=0.61 (see Table I). Factors which reduce the risk of dyslexia by 2 or more (i.e. an odds ratio of 0.5 or less) should, therefore, be detectable with the available cohorts.

PSYCHOMETRICS

Children aged 6–17 years (n=317: 180 males, 137 females) were given standard psychometric tests including British Ability Scales subtests (Elliott et al. 1983): Similarities (verbal reasoning, n=317), Matrices (non-verbal reasoning, n=312), Recall of Digits (verbal working memory, n=127), Single Word Reading (n=317), and Spelling (n=302). Results were expressed as age-adjusted T-scores with a mean of 50 (standard deviation 10). A discrepancy score (DS) was computed as follows:

Maximum (Similarities, Matrices) – Maximum (Reading, Spelling)

On this conservative criterion, children were classified as dyslexic (n=163; 107 [65.6%] males, 56 [34.4%] females) if both their British Ability Scales Reading and their Spelling scores were >20 T-score points – equivalent to 2 standard deviations (SDs) – below the maximum of their British Ability Scales Similarities and Matrices (i.e. DS>20). Individuals were classified as controls (n=154; 73 [47.4%] males, 81 [52.6%] females) if DS was less than 1 SD. The null hypothesis was that children with and without dyslexia are equally likely to have a family history of cancer.

DISEASE MEASURES

Parents of 202 families were given questionnaires asking whether they or their close relatives (not defined) had ever to their knowledge had various clinical conditions, including cancer. Individuals (n=317) were, therefore, classified as having a family history of cancer (C+; n=152) if they or a member of their family had suffered from any form of the disease; otherwise they were considered not to have a family history of cancer (C–; n=165). One of the children was reported as having cancer (malignant astrocytoma).

ANALYSIS

Groups with and without familial cancer were analyzed for differences in dyslexic:control ratio and psychometrics. The hypothesis predicts that measures of general ability (British Ability Scales Similarities and Matrices) will not differ greatly, while British Ability Scales Reading and Spelling will differ. Groups were also compared on age at date of participation (n=317), maternal (n=301), and paternal (n=292) age at date of participation, and birth order (first vs later born, n=311).

As the dyslexic and control groups were not matched on potentially confounding variables such as sex, logistic regression models were used to examine the effects of these variables on the outcome variable (dyslexic/control group membership). The first model fitted only familial history of cancer

(C+/C–). The second model also fitted potentially confounding variables (sex, birth order, age, number of children, Similarities, Matrices, parental age); these were added to the model before C+/C–. Results were similar whether 'family history' was restricted to parents and grandparents or was unrestricted, so inclusion in the family history of cancer group was based on any member of the family (up to 3 generations) having had cancer. For each independent variable, the coefficient (B), the Wald statistic (Wald), and the significance level (p value) are given. The overall percentages of correctly-predicted responses and the model χ^2 statistics for each model are also given.

STATISTICS

Pre-analysis indicated that distributions of psychometric variables were significantly non-normal (data not shown). Fisher's exact tests or χ^2 tests were, therefore, used as appropriate (for categorical data) and Mann–Whitney non-parametric tests (for numerical data). Significance was evaluated at $p<0.05$. Because of the variables' non-normal distributions, quartile values (rather than means and SDs) are given in the tables.

The odds ratio was also calculated as follows:

$$\text{OR} = \frac{(\text{number of C+ dyslexics} / \text{number of C– dyslexics})}{(\text{number of C+ controls} / \text{number of C– controls})}$$

Because the proposed association between dyslexia and family history of cancer is negative (i.e. family history of cancer may be a 'protective' factor), odds ratios are predicted to be <1.00.

To see whether there was any evidence of a 'dose-response' effect, mean psychometric scores were compared, in the group as a whole and separately by sex, using a Kruskal-Wallis test across four groups: none (no relatives reported with cancer), one, two and three or more (the highest reported was six).

FURTHER ANALYSES

Potential objections to this analysis could include:

Sex differences

The ratio of males to females was greater in the dyslexic group, as is often found in dyslexia and other learning disabilities (Gualtieri and Hicks 1985, Miles et al. 1998). As well as the logistic regression described above, the family history group comparison was repeated separately for each sex.

Report bias

Every family in the study is participating because at least one child has reading problems; however, some families mentioned more relatives than others. Analyses were therefore repeated using only data from parents and grandparents. Given the relatively young ages of participants (mean age 11 years 5 months, SD 2 years 11 months) and their parents (paternal mean age 44 years 2 months, SD 5 years 8 months, maternal mean age 41 years 5 months, SD 4 years 8 months), this is probably a conservative restriction.

Number of children

Some of the 202 families in the study have one child participating ($n=102$), others have two children ($n=87$), three ($n=11$), or even four ($n=2$). Number of children may, therefore, be a confound if, for example, dyslexics and controls have different family sizes. Ideally, 'family' should be used as a stratification factor, but resource limitations (i.e. software) prevented this. Instead, mean scores on psychometric tests were compiled for each family. The resultant scores were treated as single observations and the families with a history of cancer (including all relatives) were compared with the families with no such history, using a Mann–Whitney non-parametric statistic.

Cohort effect

There may be some feature of this selected cohort that affects associations with medical conditions in general. For example, it is possible that families with more dyslexic children might have a greater tendency to underreporting of medical conditions, due to the questionnaire approach. To control for this, the basic analyses described above were repeated using two other medical conditions included in the questionnaire: insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM). These were chosen because, like cancer, they are relatively common and are thought to have complex aetiologies with both genetic and environmental components. It is not known whether there is any hypothesis which implicates PAF directly in their aetiology, although excessive PAF has been linked to complications in NIDDM, particularly nephropathy (Kudolo and DeFronzo 1999). Therefore, it was expected that groups defined by the presence (D+) or absence (D–) of a family history of diabetes should not show significantly different proportions of those with dyslexia and control participants, or significant differences on reading and spelling ability (or indeed other British Ability Scales psychometric variables).

Post-hoc analysis

The psychometric data presented here do not facilitate differentiation between possible dyslexic phenotypes. However, a post-hoc analysis of the full dataset provided additional psychometric data for participants with dyslexia. While this cannot fully resolve the issue of differentiating the various features that have been associated with dyslexia, it may provide some initial pointers for future studies. The available measures included handedness (using the Annett pegboard task [Annett 1985]; data were available for 99/101 of those with dyslexia and C–, and 61/62 those with dyslexia and C+) and visual motion sensitivity (using random dot kinematograms [Cornelissen et al. 1995]; data available for 88/101 of those with dyslexia C–, and 56/62 of those with dyslexia and C+). Some research has suggested that dyslexia may be associated with a tendency towards mixed-handedness (Richardson and Gruzelier 1994) and with reduced visual motion sensitivity (Talcott et al. 2000).

In addition, many of the participants' parents were given the Revised Adult Dyslexia Checklist 20-item checklist of dyslexic-type symptoms, which while not a formal instrument does give some idea of symptomatology (Vinegrad 1994). Data on mothers' Revised Adult Dyslexia Checklist ratings were available for 98/101 of those with dyslexia and C–, and 61/62 of those with dyslexia and C+. Data on fathers' Revised Adult Dyslexia Checklist ratings were available for 97/101 of those with dyslexia and C–, and 62/62 of those with dyslexia and C+.

Handedness measures were the mean of five pegboard completion times for each hand, the mean for both hands, and the difference between left and right hands. Visual motion sensitivity comprised the average of two measures of the

psychophysical threshold at which coherent motion could be detected. These measures and maternal and paternal Revised Adult Dyslexia Checklist ratings were compared for participants with dyslexia with and without a family history of cancer, using Mann–Whitney non-parametric statistics.

Informed consent for collection of psychometric and medical data was obtained from all parents. Clinical assessment of children was independent of agreement to participate in the research study. Ethical approval was obtained from the local Research Ethics Committee.

Results

COMPARISON OF GROUPS WITH (C+) AND WITHOUT (C–) A FAMILY HISTORY OF CANCER

As predicted, and even when the definition of family history was restricted to parents and grandparents only, the C+ group performed significantly better than the C– group on Reading (Mann–Whitney U, $p=0.008$) and Spelling (Mann–Whitney U, $p=0.002$), but not on other measures (the reduced numbers available for Recall of Digits may have contributed to the null result for this measure). When other relatives were taken into account, the C+ and C– groups differed significantly on Recall of Digits (Mann–Whitney U, $p=0.039$, despite the reduced numbers available), Reading (Mann–Whitney U, $p=0.002$), and Spelling (Mann–Whitney U, $p<0.001$). Groups did not differ significantly on sex, age, maternal or paternal age, birth order, or number of children. Quartiles for the C+/C– groups, taking all relatives into account, are shown in Table II.

A Fisher's exact test by dyslexic status was significant ($p<0.001$): 62/163 (38%) dyslexics were in the C+ group, whereas 90/154 (58.4%) controls had a familial history of cancer. Odds ratios with confidence intervals (CI) for the C+ and C– groups are shown in Table III.

COMPARISON OF DYSLEXIC AND CONTROL GROUPS

Participants with dyslexia and controls differed significantly on sex (Fisher's exact test, $p=0.001$), Similarities, Reading, Spelling, and Recall of Digits (Mann–Whitney U, $p<0.001$), but not on other variables. Details are shown in Table IV.

LOGISTIC REGRESSION

Table V shows the results of logistic regression analyses for family history of cancer only (Model 1) and for additional variables (Model 2). According to the model χ^2 statistic, both models are significant overall ($p<0.001$), and family history remains a significant contributor even when additional variables are entered into Model 2 ahead of it (Similarities is also an important contributor). Model 1 predicted 60.25% and Model 2 predicted 70% of responses correctly. (When logistic regression models were fitted with family history of diabetes

Table II: Quartile psychometric scores for participant groups with and without a family history of cancer

Psychometric variables	*No family history of cancer (C–)*				*Family history of cancer (C+)*				*p*
	n	*25%*	*50%*	*75%*	*n*	*25%*	*50%*	*75%*	
Sex	165	1	1	2	152	1	1	2	*ns*
Birth order	163	1	2	2	148	1	2	2	*ns*
Age at visit	165	9	12	14	152	9	11	13	*ns*
Number of children	165	2	3	3	152	2	2	3	*ns*
Similarities[a]	165	56	62	69	152	55	61	68	*ns*
Matrices[a]	162	50	56	61.25	150	52	57	62	*ns*
Recall of Digits[a]	43	33	43	50	84	41	46.5	52	0.039
Reading[a]	165	37	43	50	152	38.25	48.5	56.75	0.008
Spelling[a]	153	33	42	47	149	38	46	53	0.002
Paternal age	148	40	44	47	144	39	44	48	*ns*
Maternal age	152	38	41	44.75	149	38	41	45	*ns*

[a]From the British Ability Scales (Elliott et al. 1983).

Table III: Odds ratios and confidence intervals (CI) for family history groups

Family History	*Data Restriction*	*Odds Ratio*	*CI (lower)*	*CI (upper)*
C+	None	0.44	0.28	0.68
C+	Parents/Grandparents	0.6	0.37	0.96
C+ (males)	None	0.55	0.3	0.99
C+ (females)	None	0.31	0.15	0.63
C+ (males)	Parents/Grandparents	0.72	0.38	1.34
C+ (females)	Parents/Grandparents	0.44	0.21	0.94
IDDM	None	0.84	0.33	2.13
IDDM	Parents/Grandparents	1.09	0.51	2.31
NIDDM	None	0.6	0.29	1.22
NIDDM	Parents/Grandparents	1.08	0.59	1.96

C+, participants with a family history of cancer; C–, no family history of cancer; IDDM, insulin-dependent diabetes; NIDDM, non-insulin-dependent diabetes.

only, the models were not statistically significant for either type of diabetes [data not shown]).

ANALYSIS OF PSYCHOMETRICS BY NUMBER OF RELATIVES WITH CANCER

A Kruskal-Wallis test showed that the children in the four family disease history groups (none, one, two, three, or more) differed significantly on Reading ($p=0.006$) and Spelling ($p=0.002$), but not on Similarities, Matrices, or Recall of Digits. Figure 1 shows the number of individuals classified as controls (left-hand side) or dyslexic (right-hand side) who have none, one, two, or three or more relatives with cancer. Significantly more individuals with dyslexia reported no relatives with cancer, compared with controls (χ^2 15.4 (3), $p<0.001$).

Figure 2 shows the discrepancy scores (DS) for each family history group, separated by sex. As Figure 2 illustrates, DS, which indexes the severity of reading disability, tended to decrease as the number of relatives reported as having cancer increased. The effect appears particularly noticeable in females; in males, a larger number of relatives appear to be required before the effect on DS is seen.

FURTHER ANALYSES

Sex differences

Because there are more males with dyslexia than females in the sample, the analysis of the C+ and C– groups was done separately for males and females. For males, 56.2% of controls and 41.1% of those with dyslexia were in the C+ group, a difference of 15.1% (Fisher's exact test, $p=0.05$). For females, 60.5% of controls were in the C+ group but only 32.1% of those with dyslexia were C+: a difference of 28.4% (Fisher's exact test, $p=0.002$). The ORs were 0.55 for males, and 0.31 for females. When this analysis was repeated with only parents and grandparents included, results were similar but at lower significance levels (males' OR=0.72, females' OR=0.44).

Analysis of psychometrics by family

Family mean psychometric scores were compared for C+ and

Table IV: Quartile psychometric scores for dyslexic and control group comparisons

Psychometric variables	*Control*				*Dyslexic*				*p*
	n	*25%*	*50%*	*75%*	*n*	*25%*	*50%*	*75%*	
Sex	154	1	2	2	163	1	1	2	0.001
Birth order	151	1	2	2	160	1	2	2	*ns*
Age at visit	154	9	11	13	163	9	11	14	*ns*
Number of children	154	2	2.5	3	163	2	2	3	*ns*
Similarities[a]	154	53	58	64	163	60	67	71	<0.001
Matrices[a]	150	50	55	60.25	162	52	57	63	*ns*
Recall of Digits[a]	72	42	49	54	55	36	43	47	<0.001
Reading[a]	154	48	54.5	63	163	34	38	44	<0.001
Spelling[a]	152	43	50	55.75	150	31.75	38	43	<0.001
Paternal age	142	39	44	48	150	39.75	44	48	*ns*
Maternal age	150	38	41	45	151	38	41	45	*ns*

[a]From the British Ability Scales (Elliott et al. 1983).

Table V: Logistic regression analysis for family history of cancer only (Model 1) and for additional variables (Model 2)

Psychometric variables	*Model 1*			*Model 2*		
	B	*Wald*	*p*	*B*	*Wald*	*p*
Sex	–	–	–	–0.45	2.56	*ns*
Birth order	–	–	–	0.23	0.52	*ns*
Age	–	–	–	0.05	0.65	*ns*
Number of children	–	–	–	–0.08	0.15	*ns*
Similarities	–	–	–	0.1	26.59	<0.001
Matrices	–	–	–	0	0.01	*ns*
Paternal age	–	–	–	–0.02	0.2	*ns*
Maternal age	–	–	–	–0.01	0.1	*ns*
C+	0.83	13.02	<0.001	–0.72	6.86	0.009
Constant	–0.37	5.1	0.024	–4.41	5.72	0.017
Overall % prediction		**60.25**			**70**	
χ^2		*df*	*p*		*df*	*p*
Block	–	–	–	6.98	1	0.008
Model	13.3	1	<0.001	49.42	8	<0.001

C+, participants with a family history of cancer.

C– families. Significant differences were found for Recall of Digits (Mann–Whitney U, $p=0.018$), Reading (Mann–Whitney U, $p=0.006$), and Spelling (Mann–Whitney U, $p=0.001$), but not for Similarities or Matrices. Details are shown in Table VI. When the analysis was restricted to include parents and grandparents only, significant differences were found for Matrices (Mann–Whitney U, $p=0.014$), Reading (Mann–Whitney U, $p=0.009$), and Spelling (Mann–Whitney U, $p=0.002$), but not for Similarities or Recall of Digits.

Control conditions

As expected, and whether or not the definition of family history (of IDDM or NIDDM) was restricted to parents and grandparents only, the group with a positive family history (D+) did not differ significantly from the D– group on any of the British Ability Scales psychometric measures (Mann–Whitney U, $p>0.05$). Fisher's exact tests by dyslexic status were not significant for either condition on either definition. The ORs, including all relatives/parents and grandparents only, are shown in Table III.

Post hoc analysis of participants with dyslexia

Participants with dyslexia with (C+) and without (C–) a family history of cancer were compared, using Mann–Whitney tests, on measures of handedness, visual motion sensitivity, and maternal and paternal Revised Adult Dyslexia Checklist (i.e. ratings of dyslexic symptomatology). Results found no statistically significant difference between the C+ and C– dyslexic groups for handedness or for maternal Revised Adult Dyslexia Checklist. However, significant differences were found for paternal Revised Adult Dyslexia Checklist ratings (Mann–Whitney U, $p<0.001$) and for visual motion sensitivity (Mann–Whitney U, $p=0.015$). Participants with dyslexia (D+) without a family history of cancer (C–) had higher motion detection thresholds (i.e. lower visual motion sensitivity). The fathers, but not the mothers, of C–participants with dyslexia had higher Revised Adult Dyslexia Checklist ratings (i.e. more dyslexic symptoms). Results are summarized in Table VII.

Sources of bias

Any study such as this, which uses self-report data from a questionnaire, is open to problems. A common criticism is that some individuals may be more willing to report clinical conditions than others. Individuals who themselves have a disorder may be more willing to report their clinical history; and women may be more willing to report than men. This form of bias can never be ruled out altogether in a questionnaire study. However, it is worth noting that: (1) At the time of the study, respondents to the questionnaires could not have been aware of the hypothesis tested here, as it had not been published. Both parents in families with one or more dyslexic children were asked about a large number of clinical conditions. (2) As all families were taken from a cohort already investigated for dyslexia, there was unlikely to be a bias on the basis of dyslexic status. In the study, dyslexia was discussed with participants as a physical, genetically-based condition. In that sense, all participants were already attuned to the 'medical' nature of the study, and hence (because the study concerned genetics) to the relevance of family medical history, before the questionnaires were filled in. This priming may have operated to reduce questionnaire bias. In addition, it is expected that underreporting bias would affect all medical conditions equally; however, results showed clear differences between cancer and diabetes. (3) A Fisher's exact test (data not shown for reasons of space) indicated no statistically significant difference between male and female response rates to the questionnaire. (4) C+ and C– groups did not differ significantly on age, sex, birth order, family size, or parental age, reducing the likelihood of bias due to these factors. Dyslexic and control groups did not differ significantly on age, birth order, family size, or parental age. Given

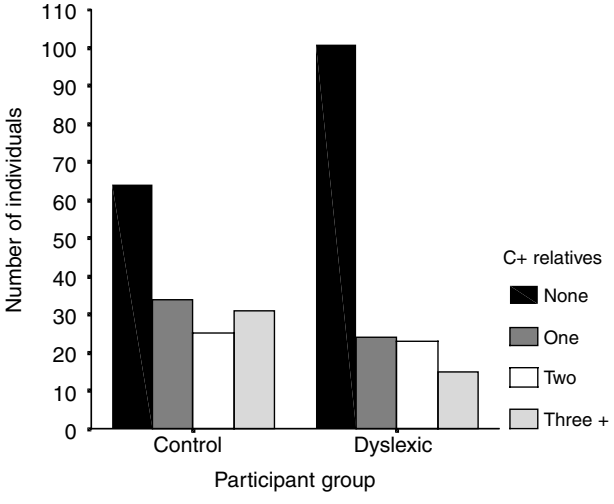

Figure 1: *Number of individuals classified as controls (left-hand side) or dyslexic participants (right-hand side) who have varying numbers of relatives with cancer (C+ Relatives): none (solid black bars), one (dark grey bars), two (white bars), or three or more (light grey bars).*

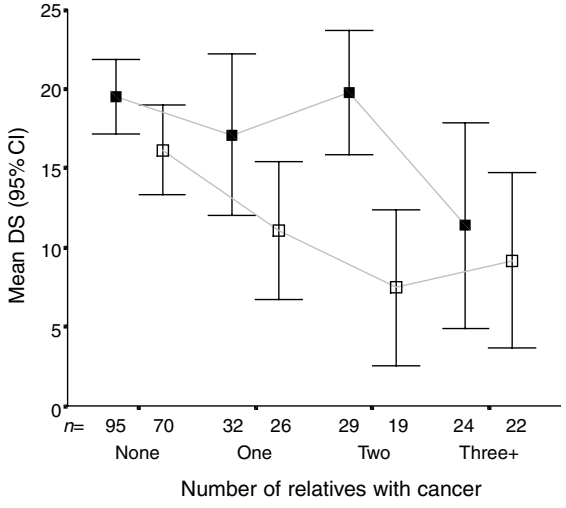

Figure 2: *Mean dyslexic discrepancy score (DS), which reflects severity of reading disability, for individuals grouped by number of reported relatives with cancer (none, one, two, three, or more). Error bars indicate 95% confidence interval.* ■ *male;* □ *female.*

that cancer rates are age-variant, the fact that groups are comparable on parental age is encouraging (grandparental ages were not available). Moreover, the families have a similar socioeconomic background and come from the same geographic area (Central Southern England). (5) One might expect that the parents of children with dyslexia are more likely to report medical conditions, including cancer, than parents of children without dyslexia because they are aware that dyslexia may have a biological basis. This potential source of bias should favour more reported cancer in the families of children with dyslexia. However, this analysis demonstrates the reverse: less reported disease in the families of children with dyslexia, with a particularly strong effect for females.

Discussion

The hypothesis that the proinflammatory mediator platelet-activating factor (PAF) may be raised in developmental dyslexia (Taylor et al. 2001) predicts a negative association between the presence of dyslexia and the presence of cancer (but not diabetes). Results of this study indicate clear differences between children with (C+) and without (C–) a family history of cancer. Consistent with the prediction, C+ children perform significantly better on psychometric tests of reading and spelling. No significant effects were found for either insulin-dependent or non-insulin-dependent diabetes. For cancer, the effect appears more noticeable in female children than in males. There is also some evidence of a 'dose' effect, in that the children of families in which more relatives have cancer show better reading and spelling performance. Again, the effect is clearer in females.

LIMITATIONS

It should be noted, firstly, that the study groups are small. One would expect this to mediate against the likelihood of finding any effects, but in fact the effects were significant and repeatable across a range of analyses. Of course, there may be additional factors (e.g. a cohort effect, lifestyle or other differences) that have not been taken into account by this study, and that could be potential confounds. However, given topics as complex as dyslexia and cancer, and the resource limitations discussed earlier, that is unavoidable.

Secondly, there was no control for familial smoking, which may affect PAF metabolism (Imaizumi et al. 1990). This is a flaw that can be rectified in future studies. However, it appears that there is no evidence currently available that people with dyslexia or their families smoke either more or less than the general population.

Thirdly, this sample is not representative of the general population. It focuses on children who are reported to have some degree of difficulty with reading, and their siblings. The socioeconomic background is middle-class, and the geographical catchment area restricted to the Southeast of England. Further research in more representative samples is required.

THE NATURE OF THE SYNDROMES

Cancer

As already mentioned, cancer is not a single disease, so a wide range of biochemical, immunological, and genetic mechanisms may be conflated by treating it as such. Some forms of cancer are thought to have a greater genetic component (e.g.

Table VI: Quartile family psychometric scores for participant groups with and without a family history of cancer

BAS subscales	*No family history of cancer (C–)*				*Family history of cancer (C+)*				*p*
	n	*25%*	*50%*	*75%*	*n*	*25%*	*50%*	*75%*	
Similarities	106	57	62	67.5	96	55.63	61.75	67	*ns*
Matrices	105	50	56	60	94	52.25	57.25	61.63	*ns*
Recall of Digits	35	33	43	50	55	42	46	50	0.018
Reading	106	38	44	50.63	96	41.25	47	56	0.006
Spelling	103	33	41	47	95	39	46	50	0.001

[a]From the British Ability Scales (BAS; Elliott et al. 1983).

Table VII: Post-hoc quartile psychometric scores for dyslexic groups with and without a family a history of cancer

Psychometric variables	*No family history of cancer (C–)*				*Family history of cancer (C+)*				*p*
	n	*25%*	*50%*	*75%*	*n*	*25%*	*50%*	*75%*	
PEGL	99	10.26	11.18	12.51	61	9.99	11.24	12.43	*ns*
PEGR	99	9.45	10.34	11.52	61	9.18	10.35	11.27	*ns*
PEGAV	99	9.73	10.77	12.05	61	9.73	10.91	11.90	*ns*
PEGDIFF	99	–1.53	–0.87	–0.16	61	–1.64	–1.00	–0.52	*ns*
VMS	88	14.15	17.83	23.84	56	10.88	15.58	20.04	0.015
Paternal RADC	97	3.00	7.00	10.00	62	1.00	3.00	8.00	<0.001
Maternal RADC	98	3.00	5.00	10.00	61	2.00	8.00	12.00	*ns*

PEGL, Pegboard test left hand; PEGR, right hand; PEGAV, mean/average; PEGDIFF, difference between left and right hands (Annett 1985); VMS, visual motion sensitivity; RADC, Revised Adult Dyslexia Checklist (Vinegrad 1994).

breast cancer in females) while others may have a greater environmental component (e.g. cervical cancer). This too should mediate against the possibility of finding significant results. Nevertheless, the results were significant, suggesting at the very least that further research may be worthwhile.

Dyslexia

Like cancer, developmental dyslexia appears to result from a combination of genetic and environmental factors and to manifest in a variety of phenotypes. That dyslexia does have a genetic component, and that changes in the brain are involved, is now widely accepted. Dyslexic symptoms can result from brain damage acquired in adulthood and are also observed in childhood conditions where the brain is known to be affected, such as cerebral palsy (Marin Padilla 1999). There is still debate over how best to define 'the dyslexic phenotype'. Some researchers argue that the known associations of dyslexia with other developmental disorders, such as dyspraxia and attention-deficit–hyperactivity disorder, suggest the existence of a spectrum of aetiologically-related conditions (e.g. Richardson and Ross 2000); others insist that dyslexia should be separated out and defined on the basis of a phonological deficit (e.g. Shaywitz and Shaywitz 1999).

The psychometric data presented in the main body of this paper do not facilitate differentiation between possible dyslexic phenotypes, but a post-hoc analysis of the full dataset provided additional data on participants' handedness, visual motion sensitivity, and parental dyslexic symptoms. Handedness did not show significant differences between C+ and C– groups, which is perhaps not surprising given the size of the cohorts. Visual motion sensitivity, however, was significantly reduced in children with dyslexia who did have a family history of cancer. It may be that any 'protection' afforded by this particular genetic background may be particularly relevant to more visual dyslexic symptoms, but much more research is needed to resolve this issue. Of particular interest is the unexpected finding that paternal, but not maternal, ratings of dyslexic symptoms were lower in children with dyslexia who had a family history of cancer. These results are consistent with a shared genetic background for dyslexia and cancer (and were not seen for diabetes in this study), but require replication with better measures of parental dyslexic symptoms.

POTENTIAL MECHANISMS

This is a descriptive study. It says little about the nature of the relationship between family history of cancer and dyslexia in children, beyond noting its apparent existence. Because the relationship appears to exist at the familial level, it is tempting to speculate that the study's initial assumption – that genetic features may underlie the observed link – is correct. These genetic features may give rise to biochemical differences which increase the risk of dyslexia while decreasing the risk of cancer. It was hypothesized that these biochemical differences may include raised levels of proinflammatory mediators, such as cytokines and platelet-activating factor, although it seems incorrect to assume that these are the only factors which are involved.

Another neurodevelopmental disorder in which a similar association has been noted is schizophrenia (Cohen et al. 2002, Lichtermann et al. 2002). Because individuals with schizophrenia have a very high rate of smoking, they show an increased risk of cancers, particularly lung cancer. However, their relatives show a decreased risk, consistent with a genetic factor whose protective effects are overridden by the lifestyle (smoking) of patients. Some authors (Lichtermann et al. 2002) suggest that immunoregulatory genes may be involved (Oken and Schulzer 1999), partly on the basis of research indicating a site on chromosome 6p21 as a potential locus (Wright et al. 1998). This locus, which incidentally is close to the tumour suppressor gene CDKN1A (OMIM 2000), has also been implicated in dyslexia (Fisher et al. 1999, Kaplan et al. 2002). Although dyslexia is obviously a much milder condition than schizophrenia, the two have been reported to share a number of similarities, including positive schizotypal traits (Claridge 1997) and abnormal visual motion processing (Cornelissen et al. 1995, Stuve et al. 1997). But there are also important differences to be taken into account when considering a potential relationship between dyslexia and cancer. For schizophrenia, Cohen and colleagues (Cohen et al. 2002) argue that institutionalization might be a mediating factor, possibly improving nutrition and reducing alcohol consumption, sexual activity, and sun exposure (all risk factors for some cancers); they also suggest an anti-tumour activity of neuroleptic medications. However, people with dyslexia are neither institutionalized nor treated with neuroleptics. Nor, it seems, do they engage in fewer risky behaviours than their nondyslexic peers.

A finding which remains to be explained is that the association with familial cancer was stronger in females. One possibility is the existence of pro-male biases such that male children are more readily diagnosed with dyslexia (Wehmeyer and Schwartz 2001). Female children whose reading problems are severe enough to receive attention may therefore carry a greater genetic load than males (Gualtieri and Hicks 1985), strengthening the association observed here. However, other possibilities, for example male–female differences in PAF levels, cannot be assessed without further research.

The instrument used in the study was a simple questionnaire asking whether parents of children with dyslexia, or any of their relatives, had ever suffered from a range of clinical conditions (including immune disorders, developmental disorders, and numerous other conditions). Given the unrefined nature of this assessment, the highly speculative nature of the original hypothesis, and the relatively small numbers in the groups, the findings were unexpectedly clear. However, it is possible that the small numbers may have affected the results (although any such effect would arguably be likely to blur distinctions rather than enhance them). A study is currently being planned to see if the result can be replicated with larger numbers, and differences in PAF metabolism detected between dyslexic and control groups. In the meantime, it is hoped that, as developmental dyslexia is now widely accepted as a brain-based physiological condition, epidemiological studies of its comorbidity with other diseases could provide much-needed clues to the underlying mechanisms involved. If replicated, these findings would cast a positive light on dyslexia, a syndrome often described in negative terms. Finally, it is possible that bridging the (until now considerable) gulf between dyslexia genetics and cancer genetics could facilitate research developments in both areas, to mutual benefit.

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List of abbreviations

C+	Family history of cancer
C–	No family history of cancer
D+	Family history of diabetes
D–	No family history of diabetes
DS	Discrepancy score
IDDM	Insulin-dependent diabetes
NIDDM	Non-insulin-dependent diabetes
PAF	Platelet-activating factor