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Investigation of Quantitative Measures Related to Reading Disability in a Large Sample of Sib-Pairs from the UK

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We describe a family-based sample of individuals with reading disability collected as part of a quantitative trait loci (QTL) mapping study. Eighty-nine nuclear families (135 independent sib-pairs) were identified through a single proband using a traditional discrepancy score of predicted/actual reading ability and a known family history. Eight correlated psychometric measures were administered to each sibling, including single word reading, spelling, similarities, matrices, spoonerisms, nonword and irregular word reading, and a pseudohomophone test. Summary statistics for each measure showed a reduced mean for the probands compared to the co-sibs, which in turn was lower than that of the population. This partial co-sib regression back to the mean indicates that the measures are influenced by familial factors and therefore, may be suitable for a mapping study. The variance of each of the measures remained largely unaffected, which is reassuring for the application of a QTL approach. Multivariate genetic analysis carried out to explore the relationship between the measures identified a common factor between the reading measures that accounted for 54% of the variance. Finally the familiality estimates (range 0.32–0.73) obtained for the reading measures including the common factor (0.68) supported their heritability. These findings demonstrate the viability of this sample for QTL mapping, and will assist in the interpretation of any subsequent linkage findings in an ongoing genome scan.

KEY WORDS: Dyslexia; sib-pair; familiality; heritability.

INTRODUCTION

Developmental dyslexia or "specific reading disability" is a condition that can be defined as the specific impairment of reading ability despite adequate intelligence and educational opportunity in the absence of any profound sensory or neurological impairment (Critchley and Critchley, 1978; Siegel, 1989). It is the most common of the childhood learning disorders with a prevalence of approximately 5–10% in school aged children (Brown, 1978; Shaywitz *et al.,* 1990). Individuals with developmental dyslexia not only have difficulty with reading but also have problems with other forms of language such as writing and spelling. The relatively high prevalence and the impact of literacy skills on everyday life demonstrate that dyslexia represents a major educational, social and mental health problem.

The nature of the core deficits in developmental dyslexia is still a matter for some debate, with different researchers emphasizing different aspects of the phenotype (Smith *et al.,* 1996). The substantial variability of the phenotype among subjects designated as affected adds to the difficulty of determining the underlying processes that cause the disorder. The concept of "affection" itself is somewhat nebulous, as many of the objective instruments underlying diagnosis are continuous in scale i.e., disability is defined in terms of arbitrary cut-off points along the continuum representing population performance on a given measure.

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Possible mechanisms underlying reading ability have been characterized in terms of phonological and orthographic (lexical vs. sublexical) processing routes. Phonological processing requires the ability to understand that words can be segmented into speech sounds and that these sounds can be mapped explicitly to letter units. Phonological processes are deficient in a majority of poor readers. Dyslexics' deficits in phonological processes can be demonstrated using tasks such as nonword naming (Wagner and Torgeson, 1987; Van Izendoorn and Bus, 1994; Rack, Snowling & Olson, 1992). Nonwords (e.g. "torlep") are lexical items that have no meaning but can be pronounced using the correspondence rules for mapping letters to speech sounds in a particular language. In contrast, orthographic processes operate in a more direct route by which familiar letter patterns (including whole words) are used to access words in the lexicon, perhaps without phonological mediation (Coltheart, 1978; Morton, 1969; Van Orden, 1987). Such a process is extremely important for developing a sight-word vocabulary and is the route used to decode irregular words (e.g., "yacht") that cannot be successfully decoded by using the phonological processor alone.

For English speaking dyslexics, the main factor underlying poor reading performance is poor single word decoding (Olson *et al.,* 1994). Single word decoding utilizes both lexical (orthographic) and sublexical (phonological) processes. Although these routes have sometimes been conceived as independent (Colheart, 1978), giving rise to particular subtypes of reading deficit, most reading models (Ehri, 1992; Seidenberg *et al.*, 1989) suggest that orthographic and phonological skills interact and that significant gains in reading vocabulary result from bootstrapping between the two processes (e.g., Seidenberg & McClelland, 1989; Ehri, 1997; Goswami 1988, Firth, 1985). Although most disabled readers, especially in non-transparent orthographies such as English, have prominent deficits in processing both phonological and orthographic information in text, several laboratories have demonstrated that small but significant proportions of dyslexic readers have primary deficits in either orthographic or phonological decoding strategies (Castles and Coltheart, 1993; Manis *et al.,* 1996; Castles *et al.,* 1999).

The evidence for a genetic involvement in dyslexia has long been established. As early as 1905 evidence of familial clustering of a condition termed "word-blindness" was presented (Thomas, 1905). Subsequently, a number of formal segregation analyses to identify the genetic model underlying the dyslexic phenotype were carried out (Hallgren, 1950; Lewitter *et al.*, 1980; Pennington *et al.,* 1991; Lubs *et al.,* 1993). However, dyslexia is likely to represent an atypically heterogeneous group of disorders (Smith *et al.,* 1996), so it is unsurprising that no consistent genetic model has been established. The genetic epidemiological evidence for dyslexia supports an inheritance pattern of a complex disorder, with reduced penetrance, phenocopies, genetic heterogeneity and oligogenic inheritance (Hallgren, 1950; Lewitter *et al.*, 1980; Pennington *et al.*, 1991; Lubs *et al.,* 1993).

Twin studies have also indicated a significant genetic influence on dyslexia-related phenotypes. A recent large twin study in Colorado suggested a proband-wise concordance rate of 68% in MZ twins compared to 38% in DZ twins (DeFries and Álarcon, 1996). Further analysis of the Colorado sample also showed substantial heritabilities for both phonological and orthographic processing (using new orthographic tasks) [$h^2 = 0.59 \pm 0.12$ and 0.56 ± 0.13, respectively; Olson, Forsberg and Wise, 1994]. This outcome is in contrast to earlier reports from smaller twin samples suggesting lower heritability of orthographic coding ($h^2 = 0.28 \pm 0.16$) than phonological coding ($h^2 = 0.47 \pm 0.14$) (Olson *et al.,* 1989; Stevenson, 1991). Bivariate genetic analyses, also carried out in the Colorado sample (Olson, Forsberg and Wise, 1994) showed that the covariance between orthographic and phonological coding deficits can be ascribed to the same genes, along with deficits in phonological awareness, thereby supporting an etiological basis for the integrative view of these processes. However, preliminary evidence from their study indicated that the uncorrelated variance between these two factors was also significantly heritable.

Due to the often imprecise and variable definition of the reading phenotype, a great deal of research has focused on the development and assessment of psychometric measures that tap the putative processes underlying reading-skill acquisition. These measures are continuous variables, reflecting individual performance across the entire reading spectrum. They are therefore ideal for investigating the genes involved through the use of quantitative trait loci (QTL) approaches.

Given the complexity of both the phenotype and the genetic etiology, it is reassuring that several groups have claimed suggestive linkages to a number of chromosomes, including 2 (Fagerheim *et al.,* 1999), 6 (Cardon *et al.,* 1994) and 15 (Smith *et al.,* 1983). Remarkably, four separate studies have replicated the finding on chromosome 6 (Fisher *et al.,* 1999; Gayán *et al.,* 1999; Grigorenko *et al.,* 1997; Grigorenko *et al.,* 2000), with

only one sample showing no positive evidence for such linkage (Field and Kaplan, 1998; Petryshen *et al.*, 2000). Nevertheless, the nature of this and other reports of replication remain unclear because different studies have analysed different phenotypes from samples ascertained under different selection criteria. Also these results cannot be viewed in the context of a sib-pair genome screen, as currently no such study has been undertaken.

To further investigate genetic influences on developmental dyslexia, a collection of sib pair families has been initiated in the United Kingdom. The study aims to recruit 200 families under the current ascertainment criteria (described below) and a further 300 families under strict single ascertainment. The ultimate goal is to analyse these families in a genome wide screen to map QTLs that underlie the dyslexic phenotype. Recently Fisher *et al.* (1999) reported replication evidence on chromosome 6p using a subset of this sample (82 sibling pairs). Analysis of a partial set of the reading measures in this study revealed evidence for linkage.

In this paper we describe the study design and the phenotypic data collected for the first set of families (including the 82 families used to replicate the chromosome 6 finding) to assist in the interpretation of any subsequent linkage findings. We present a detailed description of the sample and measures so that results emerging from analysis of this cohort may be more fruitfully compared with those already described in the US and elsewhere. Although the best way to compare the different measures across studies would be to have a sample on which all the measures had been taken, this has not been possible for comparison of UK/US samples due to different ascertainment strategies, study aims and standard language usage across samples. We also conduct some multivariate genetic analyses to further explore the relationship between the different measures and to help guide hypothesis generation for the eventual linkage analysis across the genome.

METHODS

Ascertainment of Families

The study was initially constructed as an affected sib pair design using a discrepancy measure to assign affection status. A number of additional correlated measures were also collected with the potential to be explored in their continuous scale. Here we investigate the variability for QTL screening and conduct multivariate principal components analyses to explore the correlations amongst the measures.

Traditionally, a significant discrepancy between literacy skills and other cognitive abilities has been used as a diagnosis for dyslexia (Rutter and Yule, 1975; Siegel, 1989). Following this line of reasoning, families were identified through the dyslexia clinic at the Royal Berkshire Hospital, in Reading, United Kingdom. Local GPs, school doctors and nurses, and educational psychologists were contacted regarding the reading disabilities clinic at the hospital and were invited to refer any child between 7–11 years old whose reading was markedly worse than expected given their general intelligence. Although the clinic was in an eye hospital referrals were explicitly not restricted to children with visual symptoms. As this is a secondary referral center individuals attending this clinic are likely to be of middle and upper socioeconomic status, which may in part explain why this sample has higher average IQ scores. Potential probands were administered a battery of reading and cognitive tests, taken from the British Ability Scales (BAS). Individuals were defined as probands if their BAS single word Reading t-scores were > 2 standard deviations below that predicted on the basis of their BAS Similarities (verbal reasoning) or BAS Matrices (nonverbal reasoning) scores (Elliot *et al.*, 1979; Thompson, 1982; Elliot *et al.*, 1983). Twelve cases were included based on a previous report from either a clinical or educational psychologist where an individual meet the above criteria in the past but now longer meets criteria.

Given that a proband met these discrepancy criteria, they and their family were included in the study if there was evidence (on the basis of parental reports or school history) of reading disability in one or more siblings of the proband. Eighty-nine families were identified via this procedure and a blood sample was taken from each individual for DNA extraction. Of the probands in these families 72 met criteria based on the discrepancy between their similarities score and their reading score, 5 satisfied criteria based on the discrepancy between their matrices score and reading score and the remaining 12 were included based on clinical report. Two of the 89 probands were not included in the genome screen as they refused to provide a blood sample, so in each case another affected sibling was assigned the status of proband. The number of families comprising two, three, four and five total siblings were 55, 24, 8 and 2, respectively, and all families included both parents. The families comprised a total of 224 siblings, of which 146 were male and 78 were female. The excess of males reflects the gender difference seen in the probands used to identify the families (60 males, 29 females), yielding a gender ratio of 2:1. Some studies

(Shaywitz *et al.*, 1990) have shown that a high ratio of males to females suggests bias in sample ascertainment (i.e. more males referred to clinic)

Phenotypic Measures

All sibs, irrespective of their reading abilities, were assessed on a series of eight psychometric tests. None of the tests were administered to parents. Of the eight tests, four comprised a general battery to assess literacy and cognitive ability, including tests of single word reading, spelling, verbal and non-verbal cognitive abilities. The four remaining measures were designed to selectively assess the phonological and orthographic processes involved in word decoding and included: spoonerisms, nonword reading, irregular word reading and a pseudohomophone test. These measures are described in detail below.

Literacy and Cognitive Tests

Literacy skills were assessed using a word recognition (WR) measure, a standardised British Ability Scales (BAS) test of single-word reading (Elliot *et al.*, 1979; Elliot *et al.*, 1983) suitable for individuals up to the age of 14.5 years. For older individuals the Wide Range Achievement Test (WRAT-R, revised version 1984; Jastak and Wilkinson, 1984) was used. For spelling (SPELL), either the BAS or WRAT spelling test was used depending on the individual's age (the BAS for individual's aged $\leq$ 14.5, otherwise the WRAT).

Tests of verbal and non-verbal cognitive ability were administered so that the verbal task could be used to predict the reading ability of an individual. The discrepancy between predicted and actual reading ability was then calculated for each individual (SR_Dsc). The average of both cognitive tests was used to construct a measure of general intelligence (IQ). The verbal test (SIM) comprised an oral measure of verbal reasoning. Depending on the age of the subject, this was either the BAS similarities test, valid to age 17.5 years, or the Similarities sub-scale of the Wechsler Adult Intelligence Scales (WAIS; Wechsler, 1981), which is analogous to the BAS similarities test. Non-verbal reasoning (MAT) was assessed using the BAS matrices test, again valid to age 17.5 years. As there is no corresponding test within the WAIS, no test was given to older subjects.

All of the BAS measures were converted to T-scores with a mean of 50 and standard deviation of 10, except the IQ measure, which was converted to a standard-score with a mean of 100 and standard deviation of 15. Where adult tests were used the results were converted to the equivalent scale of the BAS T-score.

The BAS tests are now some 20 years old, however, we are concerned with using these continuous measures of achievement and ability as metrics that enable us to look at relationships between literacy and intelligence skills within this sample. Therefore, although there may be error in the overall description of the sample with reference to an old population mean the relative scores between measures should be unaffected by this difference.

Specific Tests for Dyslexia

The spoonerism test (SPOON) is a measure of phoneme awareness, assessing an individual's ability to manipulate phonemes in words presented to them orally, and therefore does not involve any visual processing of print (Gallagher and Frederickson, 1995; Frederickson, 1995). The test consists of three sections, which contain increasingly difficult phoneme elisions: simple phoneme deletion and substitution (e.g., replace the first sound in 'dog' with \l\ to make 'log'); complex phoneme deletion and substitution (e.g., replace the first sound in 'lip' with the first sound in 'pig' to make 'pip'); and spoonerisms (e.g., swap the first sounds of 'little, pup' to make 'pittle, lup'). Each child was given a maximum of 3 minutes to complete each section of 10 items. The number of correct items was recorded for each section of the test.

The nonword (CCN) and irregular word (CCI) naming tasks of Castles and Coltheart (Castles and Coltheart, 1993; Coltheart and Leahy, 1996) comprise thirty words each of nonwords (e.g., torlep) and irregularly spelled words (e.g., colonel). Nonwords are not real words as they lack meaning, although they can be pronounced by applying grapheme to phoneme correspondence rules and are used to assess phonological-decoding ability. Irregular words violate the standard letter-sound conventions of English, and therefore cannot be read via the use of grapheme-phonological conversion rules alone, instead requiring the recognition of a word-specific orthographic representation followed by retrieval of the appropriate phonological form. The participants were asked to attempt to name each word presented visually to them in a list, and to proceed as quickly as possible without error. The number of words correctly read out of a total of 30 nonwords and 30 irregular words was recorded.

A pseudohomophone test (ORTHO) was also administered (Olson *et al.*, 1994). This test assesses orthographic sensitivity by measuring an individual's

ability to discriminate real words from pseudohomophones (e.g., rain vs. rane). This is considered a test of orthographic skill because phonological analysis alone cannot discriminate between the pseudohomophone and the real word target because they both yield the same pronunciation. Eighty-eight word and pseudohomophone pairs were presented on a computer screen in 18 point Geneva font. Participants were instructed to view both words and decide which one was spelled correctly, guessing where necessary. Responses were keyed into the computer by appropriate button press. The stimulus duration of each word pair was not restricted but the subjects were told that each response was being timed, and therefore it was important to proceed as quickly as possible without sacrificing accuracy. The number correct and response time was recorded by the computer for the eighty items, following 8 practice trials.

The spoonerism, nonword, irregular word, and pseudohomophone data were adjusted for age using regression coefficients obtained from a school study of randomly ascertained children in the UK (Talcott *et al.*, 2000). This study involved 358 UK school children between the ages of 7 and 12.5 years who were administered the same battery of tests in the exact manner as those given to the siblings in the present study. The resulting regression equations obtained from the school study are presented below with age given in months.

$$\text{SPOON} = 8.5499 + 0.1535 * \text{age}$$
$$\text{CCN} = 6.047 + 0.118 * \text{age}$$
$$\text{CCI} = -2.264 + 0.165 * \text{age}$$
$$\text{ORTHO} = 32.166 + 0.277 * \text{age}$$

In the present sample, residuals were calculated for each individual using these regression estimates. The age at which the test reached ceiling was estimated from the relevant regression equation for the maximum number of items correct for a particular test (e.g. the ceiling age of the spoonerism test that has 40 items was 204.9 months (17 years) based on (40-8.5499)/0.1535). All values exceeding such ceilings were considered to be the maximum value (e.g. for spoonerisms all participants age 204.9 months had predicted scores of 40) in the present analyses.

RESULTS

Descriptive Statistics

Summary statistics for the eight phenotypic measures and the two derived measures of reading discrepancy and IQ are presented in Table I for the 89 probands and in Table II for 135 co-siblings.

Table I. Summary Statistic of the 89 Probands

	Mean	Standard deviation	Skewness	Kurtosis	Missing data
WR	42.578	9.430	0.184	−0.548	0
SPELL	35.564	9.890	−0.216	−0.532	9
SIM	60.847	8.892	−0.545	−0.233	2
MAT	53.663	8.316	−0.324	−0.431	6
(IQ)	114.964	14.199	−0.417	0.378	5
(SR_Dsc)	18.359	9.497	0.014	0.301	2
SPOON	−5.932	7.483	−0.169	−0.391	8
CCN	−4.402	6.344	−0.236	−0.698	0
CCI	−6.501	6.043	−0.435	−0.262	1
ORTHO	−10.864	9.271	−1.091	0.828	13

NB: Derived measures are shown in parenthesis. SR_Dsc is calculated as the discrepancy between the British Ability Scales (BAS) reading t-score and the predicted reading t-score based on the BAS Similarities (verbal reasoning) or BAS Matrices (nonverbal reasoning) scores. IQ is defined by the average of the Sim and Mat scores. All the standised BAS literacy scores and cognitive score have a mean of 50 and a standard deviation of 10 except IQ, which has a mean of 100 and standard deviation of 15. The four measures (SPOON, CCN, CCI, and ORTHO) have a mean = 0 and standard deviation as follows taken from Talcott's normal sample SPOON (S.D. = 8.888), CCN (S.D. = 7.796), CCI (S.D. = 5.624), ORTHO (S.D. = 9.484).

Table II. Summary Statistics of the 135 Co-Sibs

	Mean	Standard deviation	Skewness	Kurtosis	Missing data
WR	46.992	9.737	−0.113	−0.412	5
SPELL	38.841	9.488	−0.392	−0.155	16
SIM	62.047	7.884	−0.357	−0.665	11
MAT	55.010	8.985	−0.164	−0.991	32
(IQ)	117.214	14.423	−0.098	−0.714	32
(SR_Dsc)	15.022	10.242	0.283	0.094	11
SPOON	−4.935	7.431	−1.064	1.584	15
CCN	−3.452	5.705	−0.824	0.975	1
CCI	−4.817	5.700	−1.053	1.807	1
ORTHO	−8.380	8.255	−1.074	1.344	20

From Table I it can be seen that the average BAS reading score (WR) for the probands (mean = 42.578) is not two standard deviations below the population mean of 50. This is because the sample as a whole has a high mean IQ, and consequently, the predicted reading ability based on the similarities (or matrices) score is higher than the population mean. Since the ascertainment criteria requires a discrepancy $>$ 2 standard deviations between an individual's predicted reading and actual reading ability, the actual reading level need not be exceptionally low to meet the inclusion criteria.

The result of this is that the group's reading level is not excessively low compared to the general population.

The average age of the probands on entering the study was 13.4 years (range 7.8–25.5 years) compared to the average age of 15.2 years (6.0–30.6 years) for the 135 co-siblings. These ages are significantly different (t-test = 3.055, p = 0.0025), though all of the measures used have been age standardized.

As can be seen in Tables I and II, several of the measures show mean differences between probands and co-siblings, including the tests of word recognition (WR: t-test = 3.337, p = 0.001), spelling (SPELL: t = 2.349, p = 0.0198), similarities and reading discrepancy score (SR_Dsc: t-test = −2.3999, p = 0.0173) and irregular word reading (CCI: t-test = 2.103, p = 0.0366). As expected, in all cases the probands were significantly lower in reading scores than the co-sibs. All of the other tests showed no significant differences (at the 5% level) between the two groups.

The coefficients of skewness and kurtosis are also given (Tables I and II) as an indication of the distribution of the measures in the two groups. For the majority of the measures these coefficients do not indicate serious skewness or kurtosis. For the measures used for ascertainment unsurprisingly the probands have a more skewed distribution than the co-sibs, though all values for these measures are relatively small. In terms of the remaining measures the degree of skewness varied between the two group with generally greater skewness in co-sibs, reflecting the negative skew associated with family based ascertainment. In addition the ascertainment measures along with spelling all displayed a platykurtotic shape in both the probands and the co-sibs, this shape was also evident in the SPOON, CCN, and CCI tests for the probands only. The SPOON, CCN, CCI and ORTHO measures in the co-sibs were more leptokurtotic in shape.

From both tables it can be seen that there is still substantial variability between individuals within this selected sample. For example, the mean for the BAS word recognition test is lower for both the proband (mean = 42.578) and co-siblings (mean = 46.992) compared to the general population (mean = 50), reflecting the deficit in reading ability in our sample. However, the standard deviation around these means is 9.430 and 9.737, respectively, in comparison to the standard deviation of 10 in the normal population. Therefore, although the distribution for word recognition is shifted toward lower values compared to the normal population, the variance about the mean remains similar. This retention of variance is promising for QTL mapping applications, where individual differences are essential. The pattern of reduced means but largely unaffected variances is also true for the other measures.

Gender Differences

A gender ratio of 2:1 (60 males: 29 females) was observed in the probands. To determine if this difference remained in the affected co-siblings, two affection criteria were examined; (1) positive diagnosis on the basis of a combination of past and current information and clinical judgement (90 definite), (2) diagnosis based solely on current measures using the discrepancy score (SIM-RT or Mat-RT > 2 SD) (87 met criteria). Clinical diagnosis of the 90 definite cases in criteria (1) comprised 62 males and 28 females giving a male to female gender ratio of 2.2:1. Of the 87 affected individuals defined on the basis of the discrepancy measure (criteria 2), 52 were male and 35 were female giving a gender ratio of 1.9:1. Thus, in this clinic-referred sample, the male bias is present in both the probands and the affected sibs.

Differences between the genders were also examined in the complete dataset. As shown in Figure 1, four of the measures revealed significant differences (5% level) including spelling, SR_Dsc, nonword reading, and pseudohomophone. For each of these measures the females performed significantly better than the males. The remaining measures of word recognition, similarities, matrices, spoonerisms and irregular word reading were non-significant at the 5% level. For some of these

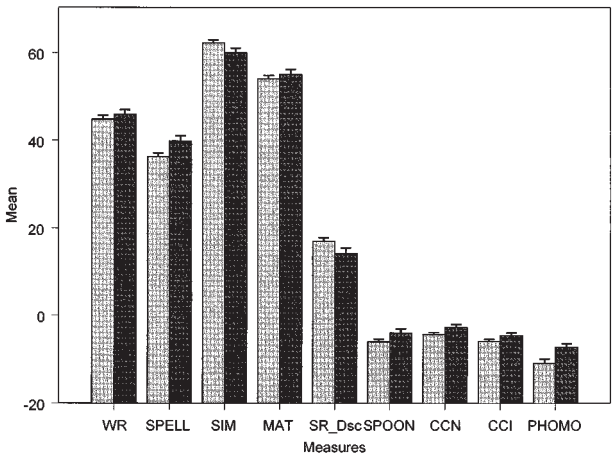

Fig. 1. Gender difference for the nine phenotypic measures (mean and standard error), males are shown in light columns; females are shown in dark columns. Significant differences (P = 0.05) were observed for SPELL, SR_Dsc, CCN, PHOMO.

measures the differences between genders may be due to the higher proportion of affected males in the sample compared to females. The analysis was then repeated taking into account the effect of IQ. IQ tests and derived measures were excluded from this analysis (SR_Dsc, Mat, Sim). For all remaining measures IQ was highly significant ($P < 0.001$). This IQ dependence did not have a substantive impact on the gender differences: spelling and the pseudohomophone test remained significantly related to gender and spoonerisms and nonword reading showed only slight changes in significance levels (0.061 to 0.037 and 0.048 to 0.056, respectively).

The discrepancy score (SR_Dsc) is one of the few measures that is significantly different between males and females in our total sample, with the males showing a greater discrepancy than the females. For the 89 probands alone, however, no significant differences between genders were observed for SR_Dsc or the measures of WR and SIM used to calculate SR_Dsc. We also examined the same measures in the co-sibs diagnosed as affected using either criteria (1) or criteria (2). Using criteria (1) none of the measures differed between males and females at the 0.05 level. Using criteria (2) WR and SIM again did not differ significantly, however, the discrepancy score (SR_Dsc) did show a gender effect (males mean = 19.047; females mean = 14.394; $t = 2.1964$, $p = 0.03$). This is due to the combination of lower average scores for verbal IQ and higher average reading levels for the females compared to the males. As the verbal IQ is used to predict the reading ability of individuals, on average, females are predicted to have lower reading ability than males. However, as their actual reading ability is consistently higher than the males, females would appear to be less discrepant readers with regard to their IQ than males. Therefore, in our study, it was easier for males to attain a diagnosis of dyslexia based on the discrepancy measure than for females. This may also account for the higher number of males in the sample compared to females.

Correlations

In order to explore the relationships among the different phenotypic measures and between the siblings, a co-sib closest in age to the proband was defined for each family and the Pearson correlation for the phenotypic measures amongst the proband and co-sib were calculated. Table III shows that the phenotypic correlations amongst the measures vary widely, with high correlations between some of the tests (e.g. word recognition and irregular word reading, $r = 0.79$, spelling and pseudohomophones, $r = 0.64$) and more modest correlations between the reading tests and specific IQ scales (range 0.25–0.39).

In the absence of shared environmental influences, the correlation of each phenotypic measure between the probands and their co-sibs provides an estimate of one-half of the (narrow-sense) heritability. These estimates are likely to be less precise compared to those obtained using more general approaches (e.g. variance components) that utilise the whole sample rather than one sibling pair per family. Still the majority of the cross-sibling correlations are in the range 0.34–0.52, with spelling having the highest familial correlation of 0.52, followed by word recognition ($r = 0.46$). The specific dyslexia measures of spoonerisms, nonword reading, irregular word reading and pseudohomophones all give very similar familial correlations of 0.34, 0.39, 0.38, and 0.36, respectively. Surprisingly, the BAS matrices measure yielded the lowest familial correlation of $r = 0.04$, which may be partly explained by the amount of missing data for this particular measure due to the lack of a test appropriate for adults. However the familialities are surprisingly low given that family based ascertainment would be expected to yield greater similarities between siblings.

Principle Components Analysis

A principle components analysis was carried out using all the sibling data, the results of which can be seen in Table IV. Two clear factors emerge from this analysis: the first factor appears to be a general reading factor (explaining 54% of the variance, eigenvalue of 2.07) with the major loadings on word recognition, spelling, spoonerisms, non and irregular word reading and pseudohomophones (loadings range between 0.357–0.416). The second factor appears to reflect a general IQ component explaining 14% of the variance (eigenvalue of 1.04). This factor is primarily defined by the similarities (0.535) and matrices (0.749) measures, with no other measure having loadings greater than 0.30 (in absolute value).

The third and fourth factor account for only 9% and 8% of the variance respectively (eigenvalues of 0.84 and 0.80). At this level the interpretation of the factors is more difficult and less meaningful.

Familiality Estimates

To extend the familial correlations between the proband and co-sibling, a formal variance component

Table III. Proband and Co-sibling Correlations

	wr_s1	**sp_s1**	**sm_s1**	**mt_s1**	**dc_s1**	**iq_s1**	**sn_s1**	**cn_s1**	**ci_s1**	**or_s1**	**wr_s2**	**sp_s2**	**sm_s2**	**mt_s2**	**dc_s2**	**iq_s2**	**sn_s2**	**cn_s2**	**ci_s2**	**or_s2**
wr_s1	1.00																			
sp_s1	0.66	1.00																		
sm_s1	0.46	0.29	1.00																	
mt_s1	0.08	0.21	0.24	1.00																
dc_s1	−0.56	−0.37	0.48	0.15	1.00															
iq_s1	0.34	0.31	0.80	0.77	0.44	1.00														
sn_s1	0.44	0.53	0.40	0.18	−0.05	0.38	1.00													
cn_s1	0.68	0.63	0.35	0.07	−0.34	0.28	0.59	1.00												
ci_s1	0.79	0.65	0.38	0.01	−0.43	0.25	0.52	0.61	1.00											
or_s1	0.59	0.64	0.44	0.19	−0.16	0.39	0.47	0.38	0.61	1.00										
wr_s2	0.46	0.31	0.13	−0.05	−0.32	0.05	0.28	0.44	0.38	0.20	1.00									
sp_s2	0.48	0.52	0.24	0.09	−0.24	0.22	0.32	0.41	0.45	0.40	0.68	1.00								
sm_s2	0.18	0.02	0.34	0.15	0.16	0.32	0.07	0.07	0.03	0.17	0.29	0.10	1.00							
mt_s2	0.15	−0.01	0.17	0.04	0.03	0.16	0.10	0.18	0.07	0.21	0.25	0.30	0.38	1.00						
dc_s2	−0.29	−0.27	0.13	0.15	0.41	0.19	−0.19	−0.35	−0.33	−0.05	−0.70	−0.56	0.48	0.06	1.00					
iq_s2	0.18	0.05	0.32	0.09	0.14	0.28	0.14	0.21	0.06	0.23	0.30	0.23	0.81	0.85	0.33	1.00				
sn_s2	0.25	0.32	0.13	0.03	−0.12	0.12	0.34	0.33	0.28	0.16	0.48	0.61	0.17	0.27	−0.32	0.25	1.00			
cn_s2	0.15	0.16	0.09	−0.12	−0.05	0.02	0.24	0.39	0.13	0.00	0.62	0.50	0.12	0.22	−0.49	0.22	0.54	1.00		
ci_s2	0.39	0.39	0.20	−0.03	−0.20	0.13	0.36	0.39	0.38	0.30	0.80	0.73	0.16	0.25	−0.61	0.26	0.61	0.57	1.00	
or_s2	0.35	0.37	0.16	−0.01	−0.19	0.12	0.20	0.28	0.32	0.36	0.66	0.59	0.27	0.36	−0.41	0.38	0.44	0.38	0.68	1.00

Key

s1, s2 refer to the proband and co-sibling respectively.

wr = WR, sp = SPELL, sm = SIM, mt = MAT, dc = SR_Dsc, iq = IQ, sn = SPOON, cn = CCN, ci = CCI, or = ORTHO.

Table IV. Principal Components Analysis

	Factor 1 "Reading" (2.07, 0.54)	Factor 2 "IQ" (1.04, 0.14)	Factor 3 (0.84, 0.09)	Factor 4 0.81, 0.08)
Measure	Loadings			
WR	0.416	−0.174	−0.205	
SPELL	0.394	−0.123	0.318	−0.169
SIM	0.249	0.535	−0.709	0.148
MAT	0.189	0.749	0.469	
SPOON	0.362		0.346	0.350
CCN	0.379	−0.196		0.533
CCI	0.415	−0.253		−0.112
ORTHO	0.357			−0.728

Loadings below |0.10| not shown.

Table V. Familiality Estimates

	No Ascertainment correction			
Measures	H^2	SE	Chi^2	p-value
WR	0.624	0.165	14.662	0.000129
SPELL	0.732	0.172	16.419	0.0000513
SIM	0.781	0.155	24.726	0.0000007
MAT	0.189	0.169	1.379	0.2403
SPOON	0.323	0.184	3.241	0.071825
CCN	0.505	0.172	8.749	0.00310
CCI	0.640	0.166	14.577	0.000136
ORTHO	0.660	0.196	10.497	0.001202

analysis was carried out to estimate familialities for each of the measures using the genetic program Pedigree Analysis Package (PAP; Hasstedt, 1984). This type of variance components approach allows the incorporation of multiple family members and the possibility to correct for ascertainment, which is of obvious importance in this study. In a sibling study such as this, estimates of genetic and shared environmental influence are confounded, so we refer to the estimates as "familialities" according to standard nomenclature. Estimates were obtained in the absence (Table V) or presence of ascertainment correction (Table VI) to explore the effects of our selection procedures.

The familiality for word recognition, spelling, similarities, irregular word reading and the pseudohomophone test are quite high (range 0.622–0.770). Nonword reading have intermediate estimates (0.496), while the spoonerisms and matrices have the lowest familialities (0.319, 0.187 respectively). Comparison of these values with the familial correlations (Table III) shows the difference that the additional 46 siblings (20% of the sample) used in the variance components approach makes to the estimates.

Table VI. Familiality Estimates

	Single ascertainment correction			
Measures	H^2	SE	Chi^2	p-value
WR	0.630	0.166	15.321	0.0004711
SPELL	0.723	0.172	16.161	0.0003095
SIM	0.793	0.153	26.266	0.000002
MAT	0.184	0.170	2.007	0.366594
SPOON	0.331	0.182	5.147	0.07627
CCN	0.510	0.172	9.232	0.00989
CCI	0.640	0.166	14.766	0.0006217
ORTHO	0.662	0.194	11.108	0.0038719

Finally the familiality for the first principle component ("Reading") was estimated to be 0.68 ± 0.160. For this analysis individuals who were missing any measures were assumed to have either the proband or co-sib mean for that measure.

The effect of adjusting for ascertainment has little effect on the familialities, indicating that the ascertainment criteria were not overly severe. However, the ascertainment criterion used was not a straightforward single selection, since only one individual (the proband) had to meet the strict criterion of the IQ/Reading discrepancy in order for the family to be included, but another sib also had to show evidence of reading problems. Thus single ascertainment correction is not likely to have fully accounted for the true selection procedure. Therefore, the familiality estimates are unlikely to accurately reflect the sources of individual differences in the general population. Our estimates are likely to be somewhat higher than the true values, as the co-sibs also had reduced values for the measures compared to the general normal population.

DISCUSSION

A battery of psychometric tests has been administered to a UK dyslexia sample ascertained via an affected proband with a family history of reading difficulties. As expected, the average proband scores on all of the reading measures are below the population mean, as are those of the co-siblings but to a lesser extent. Interestingly, however, neither the proband nor the co-sib means are exceptionally extreme, typically falling within one standard deviation of a normative school-age

sample. This finding is due in part to the IQ dependent measure used to assign a diagnosis of dyslexia in a sample where due to the ascertainment procedure individual's IQ were higher on average. This resulted in the identification of a group of individuals who are underachieving in reading related tasks with respect to their IQ but means that the sample may lack individuals who would be classed as poor readers who miss the discrepancy criteria due to an average or low IQ. Therefore the generalisability of these findings maybe limited with respect to these poor readers.

The paucity of extreme deficits in reading ability in this sample, which reflects the operational definition of dyslexia based on a discrepancy between reading and cognitive abilities rather than on reading skills alone, indicates that there is considerable variability remaining. The manifestation of individual differences, coupled with the observation of partial co-sib regression back to the population mean, suggests that the present measures of reading are influenced by familial factors that may be amenable to further genetic analysis.

The correlations between the phenotypic measures were examined, exhibiting strong relationships between some of the measures. This correlation structure was formally exploited by the principle component analysis, identifying a factor that accounts for over half of the variance in the sample and appears to be a general factor of reading ability.

We have further quantified the familial effects on the measures by evaluation of cross-sibling correlations and by maximum-likelihood model fitting. Because the sib-pair design does not lend itself to separation of genetic and environmental effects, it is instructive to compare the present findings with those from a previous twin study. The largest such study, the Colorado Twin Study of Reading Disability, estimated heritabilities for the group deficit (h^2_g) using either the same test (pseudohomophone) or similar tests for the majority of measures we have on our UK sample (Olson, Forsberg and Wise, 1994). The twin design permitted separation of the effects of shared genes (h^2_g) and shared environmental effects (c^2_g). In order to compare the estimates between the UK and US samples we need to compare the sum of these shared effects with our familiality estimates.

Results for the pseudohomophone test, a computer administered procedure developed by the Colorado laboratory, indicated a familiality estimate for the UK sample (0.66 ± 0.19) that was substantially lower than that observed in the US sample (0.85: $h^2_g = 0.56 \pm 0.13$ $c^2_g = 0.29 \pm 0.13$). This reduced familiality in the UK sample compared to the US sample was also observed for all the remaining measures that the two groups had in common. Phonological decoding, as measured by the nonword reading test gave a familiality of 0.51 ± 0.17; a similar oral nonword reading task used in the US sample, along with a silent nonword reading task, gave a familiality of 0.86 ($h^2_g = 0.59 \pm 0.12$ $c^2_g = 0.27 \pm 0.12$). For phonological awareness, the UK familiality was (0.30 ± 0.18) compared to the US (0.80; $h^2_g = 0.60 \pm 0.17$ $c^2_g = 0.20 \pm 0.16$). Again, the tests were not identical but were similar and included phoneme deletion tasks (UK, US), spoonerisms (UK), Pig-Latin (US) and an Auditory Conceptualization test (US). The word recognition task was highly familial in both the UK and the US, (UK: 0.63 ± 0.17, US: 0.95; $h^2_g = 0.47 \pm 0.09$ $c^2_g = 0.48 \pm 0.11$). The spelling tasks gave the most similar estimates of familiality, with the UK estimate (0.72 ± 0.17) compared to the US (0.84; 0.48 ± 0.11 $c^2_g = 0.36 \pm 0.11$). Higher heritabilities have consistently been found in twin studies compared to those based on nuclear families, therefore the differences in familiality estimates observed between these two studies is not unexpected (Plomin *et al.,* 1994). The general reading factor also indicated a high familiality (0.68 ± 0.160).

In the current study a gender ratio of 2:1 exists in the probands, and a similar ratio was observed in the affected siblings. Some studies suggest as much as a three to four times higher prevalence of dyslexia in males than females (Finucci *et al.,* 1983; Vogel *et al.,* 1990). However, the gender ratios observed in recent studies of research-identified samples of children with reading disability do not differ substantially from 1:1 (Shaywitz *et al.,* 1990, Guerin *et al.,* 1993; Lubs *et al.,* 1993, DeFries and Alarcon, 1996). These findings suggest that the excess of males seen in referred and clinic samples of children with reading disabilities reflects, at least in part, a referral bias (Finucci and Childs, 1981; Vogel, 1990). A somewhat higher gender ratio of 1.7:1 was observed in the affected siblings of probands with various speech and language disorders in a study by James (1992), so it is not entirely clear that referral bias explains all gender differences.

In some studies a slight over representation of males still remains even when referral bias is accounted for. It has been suggested that this may be due to the discrepancy between reading level and IQ (Lambe, 1999; Ackerman and Dykman, 1993; Feldman *et al.,* 1995; Gross-Glenn *et al.,* 1995). The use of a discrepancy score of predicted reading ability based on IQ and actual reading ability as the criteria to diagnose dyslexia has been criticised. One study showed a sig-

nificant positive correlation between the IQ of the children and the socioeconomic status (SES) scores of their parents, furthermore they demonstrated a decline in mean IQ scores for older children (Siegel and Himel, 1998). Therefore the gender differences observed in this sample are most likely due to referral bias and the use of the reading/IQ discrepancy measure, both of which have been shown in previous reports to result in an overrepresentation of males compared to females.

A genome screen is currently underway using this UK sample and this paper describes the phenotypes collected in these families. The familialities of each of the measures and the amount of variance remaining bodes well for QTL studies and demonstrates that discrete assessment may be inappropriate for capturing the etiologic complexity of reading disability. A subset of this sample has already been used to replicate the finding on chromosome 6 with some of the measures. This detailed description of the phenotypes was carried out to assist in the interpretation of any subsequent linkage findings. It is hoped that by better understanding the complex phenotype of dyslexia the underlying genes will become more accessible to mapping techniques.

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