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Developmental Dyslexia – Recurrence Risk Estimates from a German Bi-Center Study Using the Single Proband Sib Pair Design

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Key Words
Dyslexia · Genetics · Reading disability · Recurrence risk · Risch's lambda · Single proband sib pair design

Abstract
Objective: Several studies have demonstrated a genetic component for dyslexia. However, both segregation and linkage analyses show contradictory results pointing at the necessity of an optimal ascertainment scheme for molecular genetic studies. Previously, we have argued that the single proband sib pair design (SPSP) would be optimal. The aims of this paper therefore are to demonstrate the practicability of the SPSP design and the estimation of recurrence risks for reading and writing. ***Methods:*** We assessed spelling and reading in a family sample ascertained through the SPSP design. 287 families with at least two siblings and their parents were recruited. At least one child was affected with spelling disorder according to a one standard deviation (1SD) discrepancy criterion. ***Results:*** Mean values for probands and their siblings were different for both the spelling and the reading phenotype. For the probands, variances of the phenotype spelling were smaller. These effects became stronger with more extreme selection criteria. Both siblings fulfilled the 1SD criterion for spelling and reading in 60.3 and 28.9% of the families, respectively, indicating a low cost efficiency of the double proband sib pair approach. A recurrence risk of 4.52 (CI: 4.07–4.93) was obtained for spelling when the 1SD criterion was applied to both siblings. Recurrence risk estimates were similar for reading. ***Conclusion:*** The study demonstrates the suitability of the SPSP design for genetic analysis of dyslexia. The recurrence risk estimates may be used for determining sample sizes in gene mapping studies.

Introduction

Genetic Background

Dyslexia is a specific disorder in learning to read and spell in spite of adequate educational resources, normal intelligence, no obvious sensory deficits, and adequate sociocultural opportunity. Dyslexia occurs in all alphabetic orthographies, and especially spelling disorder often persists into adulthood. Affecting about 5% of school-aged children, dyslexia is the most common learning dis-

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order [1, 2]. Twin studies have repeatedly shown concordance fractions for dyslexia being higher in monozygotic than in dizygotic twins, indicating a strong genetic component with 50–70% of variation attributable to genetic factors [3]. Dyslexia tends to run in families, a finding noted for the first time at the beginning of the last century. Family studies revealed a familial aggregation of dyslexia with a familial recurrence of about 40–50% [4]. The analysis of familial patterns suggested a higher risk for siblings and parents of a child disabled for reading and spelling independent of the child's orthography. However, estimates of the recurrence risk of dyslexia are still lacking.

Instead, formal segregation analyses for both the clinical entities and quantitative traits have been undertaken to identify the genetic model underlying dyslexia. The results were quite contradictory, and no consistent genetic model has been found. For example, Lewitter et al. [5] demonstrated compatibility with a major recessive gene for reading disability for families with female probands and rejected all other major gene models, while Pennington et al. [6] showed an additive or dominant major gene effect for dyslexia in three of four samples. Since dyslexia generally does not segregate in a simple Mendelian fashion but needs to be interpreted as a complex genetic disease with reduced penetrance, phenocopies, genetic heterogeneity and oligogenic inheritance [5–10], the inconsistent results are not surprising as the assumptions imposed by segregation analyses are questionable [compare e.g. 11].

Discrepant findings have also been observed for linkage analyses. Summing up, possible loci have been identified on chromosomes 1 [12, 13], 2 [3, 14], 6 [15, 16], 15 [15, 17], and 18 [18]. Exemplary for discrepant results are linkage analyses to chromosome 6p23-p21.3: Cardon et al. [19] reported linkage of dyslexia to this region which could not be replicated by other groups [20, 21]. An obvious explanation is a false positive finding, especially since the original result was weakened later on [22]. Alternatively, results may diverge because different ascertainment criteria were applied, leading to different subsamples of dyslexia being investigated in the respective studies. This argument is strengthened by recent positive reports, see e.g. ref. [23] and citations therein.

Sampling Strategies

Dyslexia is a clinical entity that can be derived from a subject-specific score on quantitative reading and/or spelling measures. It may thus be interpreted as one tail of the distribution in reading and/or spelling abilities [24].

Since it has been shown clearly that dyslexia is a complex genetic disorder, special attention has to be paid to the planning of the design for studies aiming at unraveling the genetic basis of the disease [see 10, for a detailed discussion see 24]. To uncover the molecular genetic basis of dyslexia, sib pair analysis is a standard method. It might be preferred over the phenotyping of whole multigenerational families for several reasons [24], one of them being the lack of standardized tests for phenotype definition in adults. Furthermore, reading and spelling abilities in adulthood have been shown to be influenced by confounding variables such as job selection [25]. If, for example, a dyslexic person chooses a job where the requirements to read and write are low, his reading and writing abilities would further deteriorate, leading to an underestimate of the possible reading and spelling competence. Consequently, recruitment of children and adolescents may be preferred. Other designs that ascertain only children and adolescents in extended pedigrees include e.g. first cousin pairs. Sib pairs may be, however, preferable when there is higher compliance within nuclear families. Furthermore, these studies possibly overcorrect for environmental factors with the hope that positive findings are true. Finally, in our study (see section Materials and Methods) we have included only those families where both parents have been available for genotyping. This decreases dependency on marker allele frequencies and allows a simple application of association methods.

Generally, there are three possibilities to recruit sib pairs for genetic studies which have been contradictorily discussed regarding their efficiency, that is, sample size and screening costs as well as power. The first method is to draw sib pairs randomly from the general population. Secondly, sib pairs may be ascertained via one sibling that has an extreme value regarding the trait of interest (single proband sib pair – SPSP). Several authors have shown that the SPSP design generally results in greater statistical power in linkage analyses compared to random sib pair sampling [for an overview see ref. 26]. Thirdly, the double proband sib pair design may be employed where both siblings have extreme trait values from the top or the bottom tail of the trait distribution. As shown by several authors, extremely discordant sib pairs (ED), where one sib has a phenotype in the top tail, the other in the bottom tail of the distribution, have the greatest power to detect linkage for most simple monogenic models [27]. However, the ED approach generally results in higher rates of non-paternity [28]. In addition, practical concerns are brought forward when aiming at minimizing the total study cost [26, 29]. Under oligogenic models, both ex-

treme sib pair approaches may be counterproductive and yield a decrease in power [30]. Furthermore, extreme sampling is restricted to the consideration of a single phenotype. If several traits are of interest within a genetic study, greater practicability is generally achieved upon use of the SPSP design [24]. Thus, only a relatively small number of sib pairs usually fulfill the inclusion criteria for a second trait of interest when recruitment of extreme sib pairs is based on a different phenotype. Consequently, we concluded from theoretical considerations that the SPSP design is optimal for investigating dyslexia related traits [24].

The first aim of this manuscript therefore is to demonstrate the practicability of the SPSP design for linkage analyses in dyslexia with data from a German bi-center study. To the best of our knowledge, our study is the first utilizing a SPSP recruitment design for dyslexia and dyslexia related phenotypes. For example, Cardon et al. [19] analyzed dizygotic twins with at least one being reading disabled; however, the twins had been selected retrospectively from a larger sample recruited independent of their affection status. This may have an effect on the recurrence risk estimates. Marlow et al. [31] included families if there was evidence of reading disability in one or more siblings of the proband whereas Petryshen et al. [21] ascertained two dyslexic siblings thus not representing a true SPSP design. In our study, families are selected based on the probands' spelling score. It has been shown previously that this selection will also affect the distribution of the siblings' spelling score [32]. Furthermore, we hypothesized that the ascertainment of probands with respect to spelling and the correlation between spelling and reading affects the distributions of reading in both the probands and the siblings.

Recurrence Risks

Allison [33] has pointed out the importance of Risch's λ values [34] and emphasized their utility in the planning stage of family-based linkage studies. For example, Guo and Elston [35] have proposed optimal two-stage designs for locating disease genes by linkage studies using ED and EC sib pairs. This approach has been implemented in DESPAIR which is freely available at http://darwin.cwru.edu/despair. Similarly, we have developed and successfully applied optimal group sequential study designs for linkage analysis of complex genetic disorders based on λ values [36, 37].

Kruglyak and Lander [38] determined the required number of pairs to narrow down a chromosomal region containing a disease locus by using λ values. Finally, they were also able to estimate the probability that the putative disease gene does not lie in the surmised region in a sib pair study [39].

The concept of relative risks has been generalized for linkage analysis of quantitative traits based on extreme sib pairs by Gu and Rao [40]. Using simple monogenetic models these authors have shown analytically that a more extreme case definition increases the generalized risk ratio (GRR). Allison et al. [33] and Ziegler et al. [41] estimated generalized λ values for human obesity and demonstrated an increase of the GRR with extremer case definitions for this specific phenotype.

One purpose of this paper therefore is to provide estimates of GRRs λ_S for siblings using varying thresholds for the underlying quantitative trait. We expect an increase of λ_S with use of more extreme thresholds for definition of a case.

Material and Methods

Families

In a bi-center study, families with at least two siblings of whom at least one was affected with spelling disorder were recruited in the outpatient departments of the Departments of Child and Adolescent Psychiatry and Psychotherapy of the Philipps-University in Marburg and the Julius-Maximilian University in Würzburg. From August 2001 until April 2004 all dyslexic children were investigated at one of the Departments of Child and Adolescent Psychiatry with standardized and unstandardized tests and a family history and medical history was collected. To evaluate whether the proband or a sibling has symptoms of ADHD, a standardized clinical interview (DIPS, based on ICD-10 criteria for ADHD) was performed with the mother. If the proband or a sibling fulfilled the diagnostic criteria of ADHD based on the interview data the family was excluded from this study. A reason for exclusion of comorbid children with dyslexia and ADHD or siblings with ADHD was firstly that both traits might overlap [42]. Secondly, symptoms of inattention and hyperactivity might influence child behavior on the neuropsychological and neurophysiological examinations.

In our study, families are included if at least one child – the proband – fulfills the criterion for spelling disorder, and if there is at least one full sibling willing to participate. Spelling ability was measured by a grade-appropriate German spelling test (writing to dictation) for the children [43]. Since a spelling disorder can be reliably diagnosed soonest at the middle of the second grade, only children at least at the middle of the second grade who visited a regular primary school – no special school, e.g. for learning disabled children – were included in the study. The selection of probands is based on the spelling score which is normally T distributed with mean $\mu = 50$ and variance $\sigma^2 = 100$ in the general population, abbreviated by $T \sim N(50, 100)$. The other inclusion criteria for the study in both probands and siblings are: IQ $\geq$ 85, normal peripheral hearing and seeing, no bilingual education, no medication, and age up to 21 years. In addition, both parents had to be available for participation. For the work presented in this paper, we randomly

selected one sibling to the proband if more than one sibling was available due to the low number of families with two or more siblings to the proband. Our selection may have led to a power loss and bias [44]. However, due to the low number of families with more than one sibling, we expect these problems to be negligible.

All study participants or, in case of children younger than 14 years, their parents gave written informed consent to study participation. The study was approved by ethics committees of the universities Marburg and Würzburg.

Phenotypes

Spelling was measured using age appropriate tests rendering T scores that are distributed as N(50, 100) in unaffected children [4]. The non-verbal intelligence quotient (IQ) was assessed using the Culture Fair Test [CFT-1 or CFT-20, see refs. 45, 46] depending on the probands' age. Additionally, all probands and their siblings from second to fourth grade performed a standardized single-word reading test [Salzburger Lese- und Rechtschreibtest, 47]. This test also renders T scores that are distributed as N(50,100) in unaffected children [47]. Since there are no standardized German reading tests for children at or above the 5th grade, an unstandardized word reading test was administered in these children [48]. This test requires children to read a list of 48 words as accurately and quickly as possible. The resulting variable is the number of words read correctly within one minute. For this test, population data and age corrections were not available.

None of the tests was administered to parents.

Criteria for Dyslexia

The diagnosis of dyslexia was based on the spelling score using the T distribution of the general population. For inclusion in the study, the following discrepancy criterion had to be fulfilled by a proband: based on an assumed correlation between IQ and spelling of 0.4 [4], an expected spelling score was estimated. A child was classified as affected if the discrepancy between the expected and the observed spelling score was at least one standard deviation.

To investigate the effect of different diagnostic criteria, children were classified as affected if their spelling score was less than or equal to a critical value.

Statistical Analyses

For spelling and for the IQ tests, grade specific corrections and age corrections, respectively, were available. Hence, individual values were transformed into grade or age corrected scores. To adjust for age in the reading test, we modeled the relationship between test scores and age by applying fractional polynomials [49] in the unaffected and used the residuals transformed to a $T \sim N(50, 100)$ for further analyses.

For the analysis of GRRs for spelling in siblings [40], the risk ratio λ_S for siblings was calculated in families with an affected proband and applied using the same criterion to its sibling. No data on the required population prevalence K were available for the discrepancy criterion. We therefore estimated K by assuming that the expected spelling score was distributed similarly as the true score, so that 15.86% of the population reach a discrepancy of $\geq 1 \cdot \sigma$. In addition, we presumed that the discrepancy was independent of the IQ, and that 84.13% of the study population had an IQ ≥ 85. Taken together, we estimated the proportion of the population fulfilling the discrepancy criterion with a normal IQ to $0.8413 \cdot 0.1586 = 0.1335$. As λ_S becomes smaller with greater prevalence estimates, we additionally calculated GRRs using a conservative estimate of K = 15.86%. For the percentile criterion, K was defined as the respective quantile of the phenotype distribution.

For the analysis of GRRs for reading in siblings, the risk ratio λ_S for siblings was calculated in families with an affected proband and the same criterion was applied to its sibling. The population prevalence K was determined using the respective percentile from the normal distribution.

GRRs λ_S were calculated using all sib pairs with an affected proband and identical thresholds for both sibs. As a consequence of using different criteria, fewer probands were classified as affected with stricter criteria; hence fewer sib pairs were used for the analyses. Therefore, a trend test was carried out for λ_S using the inverse estimated standard error as weight.

Ninety-five percent confidence intervals for the GRRs λ_S were estimated using the 2.5 and 97.5% quantiles which have been obtained from a nonparametric bootstrap with 1,000 replicates.

To test the distributional hypotheses, estimates of μ and σ^2 for the performed tests were calculated separately within probands and their siblings. In addition, mean values were investigated for differences between probands and sibs applying two-sided t-tests for dependent samples. Variation within probands and siblings was compared using a homogeneity of variance test statistic for dependent samples, as described in detail by Sheskin [50]. To account for a possible deviation from normality, a nonparametric bootstrap was carried out for the homogeneity of variance test statistic with 100,000 replicates.

Where possible, values were compared with population values. Different criteria for classification as affected were used as described above with the discrepancy criterion as well as percentiles varying from 25 down to 2.5.

Results

Altogether 287 sib pairs were available for the analyses. In the probands, the empirical mean (M) and standard deviation (S) of age were M = 12.13 and S = 2.29, respectively; in their siblings the respective values were M = 13.24 and S = 3.21. Seventy-six (26.48%) of the probands and 147 (51.22%) of their siblings were females. Mean IQs in probands and siblings were M = 109.86 (S = 12.23) and M = 111.70 (S = 12.32), respectively. Upon use of the percentile criterion, the number of sib pairs with an affected proband ranged from 277 for the spelling score $\leq$15th percentile to 145 for the spelling score $\leq$2.5th percentile criterion.

Calculation of Generalized Relative Risk Ratios for Spelling and Reading

Applying the 1SD discrepancy criterion, a GRR λ_S = 4.516 (CI 4.072–4.943) was obtained for spelling. Under the conservative prevalence estimate, the value was λ_S = 3.799 (CI 3.426–4.159).

Table 1. Recurrence risk ratios for spelling and reading

Criterion for affection		Spelling			Reading		
percentile	T value	n	λ	95% CI	n	λ	95% CI
≤15.0	≤39.6	277	3.032	2.635–3.437	195	2.667	2.205–3.149
≤10.0	≤37.2	257	3.813	3.217–4.437	182	3.516	2.825–4.257
≤7.5	≤35.6	243	3.676	2.940–4.487	165	4.202	3.269–5.225
≤5.0	≤33.6	209	4.880	3.748–6.160	136	5.735	4.250–7.410
≤2.5	≤30.4	145	6.621	4.360–9.448	101	7.921	5.016–11.564
Discrepancy							
1 SD		287	4.516	4.072–4.943			
1.5 SD		270	7.644	6.579–8.735			

The T value is derived from the percentile by assuming a normal distribution for the T with mean 50 and standard deviation 10. SD = Standard deviation; n = number of sib pairs; λ = generalized recurrence risk in sib pairs; 95% CI = 95% confidence interval.

Table 2. Results for spelling and reading in affected probands and their siblings applying different affection criteria for spelling

Criterion for affection		Spelling						Reading					
percentile	T value	mean			standard deviation			mean			standard deviation		
		μ_P	μ_S	p	σ_P	σ_S	p	μ_P	μ_S	p	σ_P	σ_S	p
≤15.0	≤39.6	29.3	40.8	<0.0001	5.6	9.3	<0.0001	34.9	44.5	<0.0001	11.2	12.1	0.1919
≤10.0	≤37.2	28.6	40.7	<0.0001	5.2	9.2	<0.0001	34.1	44.5	<0.0001	10.9	12.3	0.0482
≤7.5	≤35.6	28.2	40.4	<0.0001	5.0	8.9	<0.0001	33.7	44.3	<0.0001	10.8	12.4	0.0280
≤5.0	≤33.6	27.2	40.2	<0.0001	4.7	9.3	<0.0001	32.5	44.2	<0.0001	10.4	12.5	0.0070
≤2.5	≤30.4	25.0	38.5	<0.0001	4.1	9.4	<0.0001	30.7	42.3	<0.0001	10.1	11.9	0.0475
Discrepancy													
1 SD		29.8	41.2	<0.0001	6.0	9.5	<0.0001	35.1	44.6	<0.0001	11.2	12.0	0.2350
1.5 SD		29.2	40.9	<0.0001	5.7	9.3	<0.0001	34.5	44.4	<0.0001	10.9	12.1	0.0811

μ_p = Mean values in probands; μ_S = mean values in siblings; σ_P = standard deviation in probands; σ_S = standard deviation in siblings; p = p value.

Using the different percentile criteria, resulting λ_S with 95% CI are shown in table 1 for spelling and reading, respectively. It can be seen that both λ_S for spelling and reading increase with stricter criteria as hypothesized (both trend test $p < 0.0001$).

Distribution of Spelling and Reading Scores in Probands and Their Siblings

Mean values and standard deviations for reading and spelling are shown in table 2, separately for probands and their siblings as well as for different affection criteria. It was hypothesized that $\mu_P < \mu_S$. This hypothesis is supported by the observed data for both, reading and spelling (see table 2 for details and p values). For spelling, the initial hypothesis $\mu_S < 50$ is also supported ($p < 0.0001$).

In addition, we expected the variance in probands to be reduced compared to siblings, i.e. $\sigma_P < \sigma_S$. Pronounced differences were only observed in the variance for the ascertainment phenotype spelling (table 2). However, a tendency for a reduced variance in probands compared with siblings was also observed for reading.

We furthermore hypothesized that the effect of the study design on the distribution of the phenotypes would be stronger with more extreme affection criteria. Inspection of the data clearly shows that the shift of mean spelling values away from the population mean becomes greater in both probands and siblings (table 2). Again, our expectations concerning reduced variances were not completely fulfilled (table 2).

Discussion

Twin and family studies as well as segregation, linkage, and association studies clearly indicate a strong genetic component for dyslexia. However, estimates of recurrence risks for dyslexia have not been available. In 2001, we started a German bi-center study to assess reading and spelling and a wide variety of phenotypes that are more or less closely related to dyslexia [see e.g. 2].

In our study, we employ a SPSP design, an approach that has not been used as recruitment scheme for studies in dyslexia before. Thus our first aim was to examine the efficiency of this approach.

For inclusion in our study, we selected probands based on a discrepancy criterion between the observed and the spelling score predicted by the IQ. Assuming a genetic component in the etiology of dyslexia, we expected that this ascertainment scheme affects the distribution of the siblings' spelling score. Since spelling and reading scores are correlated, we also hypothesized deviations from the normal distribution in the probands' and siblings' readings scores. Inspection of mean spelling and reading values supported the hypothesized distributions. Variances were significantly smaller in probands compared with siblings for spelling only ($p < 0.0001$). However, the tendency was similar for reading ($p = 0.08$ for the 1.5 SD discrepancy criterion). This increased variability indicates that our sample has more similarities with a random sib pair sample than a SPSP sample for the phenotype reading.

The distribution of the scores clearly shows the impracticability of the double proband sib pair approaches when focusing on a variety of traits [24]: while the number of sib pairs being affected is 173 (60.3%) for spelling, only 83 (28.9%) affected sib pairs would be available for reading out of the recruited 287 families. Therefore, the double proband sib pair approach clearly seems inefficient in our setting.

As a second aim, we examined GRRs for siblings of affected probands to be dyslexic with varying thresholds for the underlying quantitative trait [40]. Based on the data from the present study, large GRRs in siblings for dyslexia were obtained. Applying a conservative estimate for population prevalence and the 1 SD discrepancy criterion, the risk for dyslexia is more than 3.5-fold increased for children with an affected sibling as compared to the general population. Thus, our data clearly is another indication for a strong genetic component of dyslexia. The observed GRR λ_S values are similar to those reported for other complex genetic diseases such as obesity [33, 41].

We specifically hypothesized that the genetic component, hence the GRR, would be greater in families with more extremely dyslexic children. Our results affirm this assumption: λ_S is 4.89 (3.75–6.16) and 6.62 (4.36–9.44) for spelling if only the top 5 and 2.5%, respectively, of the population were regarded to be affected. Similar results hold for reading.

The statistical models used in this study were relatively simple. However, we refrained from applying the more complicated formal segregation analyses to the data available since results from previous studies were quite contradictory, and no consistent genetic model was found. This is not surprising as the assumptions imposed by segregation analyses are questionable [compare e.g. 11]. Furthermore, the sib pair design does not have enough degrees of freedom to estimate the necessary number of parameters for a segregation analysis, and is therefore intrinsically unsuitable for such an analysis.

In summary, we have shown that the SPSP design is appropriate. Furthermore, we provided GRRs λ_S for spelling and reading that allow the calculation of sample sizes in genetic linkage studies.

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