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In Search of the Perfect Phenotype: An Analysis of Linkage and Association Studies of Reading and Reading-Related Processes

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Abstract

Reading ability and specific reading disability (SRD) are complex traits involving several cognitive processes and are shaped by a complex interplay of genetic and environmental forces. Linkage studies of these traits have identified several susceptibility loci. Association studies have gone further in detecting candidate genes that might underlie these signals. These results have been obtained in samples of mainly European ancestry, which vary in their languages, inclusion criteria, and phenotype assessments. Such phenotypic heterogeneity across samples makes understanding the relationship between reading (dis)ability and reading-related processes and the genetic factors difficult; in addition, it may negatively influence attempts at replication. In moving forward, the identification of preferable phenotypes for future sample collection may improve the replicability of findings. This review of all published linkage and association results from the past 15 years was conducted to determine if certain phenotypes produce more replicable and consistent results than others.

Keywords

Specific reading disability; Linkage studies; Association studies; Phenotypes; Replications

Introduction

This special issue on the genetics of Learning Disabilities (LD) in general and specific reading disabilities (SRD) in particular was compiled with the hope of reaching a large audience. Thus, it is important to contextualize the work presented in this special issue in the field at large. Multiple excellent reviews of recent advances have been written, but their primary focus is on the molecular aspects of the work, examining the convergence of the

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data on the same chromosomal regions, genes, and specific variants within these genes (Scerri and Schulte-Körne 2010; Smith et al. 2010). This review is different in that it focuses not on the genome regions and genes, but on the phenotypes that have been engaged in the study of SRD. Although the focus here is on SRD, arguably, many of the issues discussed below are relevant to LD in general.

Specific reading disability, reading, and reading-related processes

Specific reading disability refers to challenges associated with the mastery of reading. The prevalence estimates of SRD are roughly 5–10% (Elliott and Grigorenko 2011). Children with SRD are characterized by difficulty with accurate printed word recognition, and subsequent difficulties with reading fluency and comprehension likely resulting from the initial difficulty of processing single words (Fletcher 2009). It is commonly assumed that indicators of reading and reading-related processes are distributed quantitatively on the normal curve, so that the upper tail constitutes high or able and the lower tail—low or disabled levels of performance. Correspondingly, it is hypothesized that reading ability (i.e., typical reading) and disability (i.e., atypical reading)—reading (dis)ability—are driven by the same etiological factors. Individual differences in both typical and atypical reading as well as reading-related processes have been shown to be controlled, to a substantial degree, by genetic factors; the heritability estimates for a variety of these processes typically fall in the range of 40–60% (Grigorenko 2004). The theories of and diagnostic approaches to SRD have evolved to incorporate the role of multiple cognitive components and skills (e.g., phonemic awareness (PA), phonological decoding (PD), single-word recognition, spelling) whose function is supported by specific neurobiological pathways, the formation and maturation of which are driven by a complex interplay of risks factors anchored in the genome and the environment (Fletcher 2009).

Genetic linkage and association

Although the familial and heritable nature of SRD has been realized since its emergence in the literature in the late nineteenth/early twentieth century (Hinshelwood 1907; Morgan 1896; Stephenson 1907), the era of moleculargenetic research in the etiology of SRD is relatively young, being only in its third decade (Smith et al. 1983). The majority of such studies have used genetic linkage and association analyses to explore correlations between risk gene variants and indicators of reading (dis)ability. Specifically, linkage analysis identifies genetic sections of DNA inherited by affected family members at a frequency above chance. The genetic markers analyzed are not necessarily risk variants themselves, but they “mark” regions of DNA that appear, based on statistical analyses, to be inherited together and may contain risk genes. Statistically, significance is expressed with a LOD (log of the odds likelihood of linkage) score which is considered to be definitive at LOD ≥ 3.6 or a *P*-value of ~.000022 or 10^{-5}, and suggestive at LOD ≥ 2.2 or a *P*-value of ~.000741 or 10^{-3} (Lander and Kruglyak 1995). Linkage analysis[1] is more powerful statistically when applied to multigenerational families with a high density of affected individuals and is especially useful for finding rare alleles that segregate within particular families. The disadvantage of linkage is that the findings may not be generalizable to more than one family and that the power and methods for the refinement of the gene location are limited. In contrast to linkage analyses, in which family material is crucially important, association analyses can be done with or without family material. Association analyses[2] capitalize on

[1]There is a variety of approaches to conducting linkage analyses in the field and a number of them have been applied to SRD and reading-related phenotypes. Generally speaking, there are two large classes of these analyses, parametric and nonparametric, each class being exemplified by a variety of statistical software. Of note is that statistical tests utilized by various software differ, and these tests and corresponding *P* values are not directly comparable to each other.

[2]Similar to linkage analyses, there are multiple ways to carry out association analyses. Once again, various statistical tests and resulting *P* values might or might not be comparable directly.

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the frequency of a particular genetic variant (i.e., a particular allele at a particular polymorphic site) in independent samples of unrelated cases and controls, or across families (typically trios) of probands, to identify common risk alleles within a population. This method allows for more refined searching of specific “risk” (or “protective”) variants. One disadvantage of association studies, when they are conducted within the case–control paradigm, is that they are particularly vulnerable to producing false positives as a result of ethnic (or some other) population stratification and/or multiple testing. As a result, replication is particularly important for these studies (Ioannidis et al. 2001).

Phenotypes

Participants in genetic studies of SRD undergo reading related assessments and are phenotyped with either a dichotomous qualitative label (e.g., “Affected”, “Dyslexia”, “Reading Disability”) or continuous quantitative (or component) phenotypes based on individual component measures. The five most prevalent measures in the literature are Phonological Awareness (PA), Phonological Decoding (PD), Orthographic Coding (OC), Single-Word Reading (SWR), and Spelling Ability (SA).

Phonological Awareness refers to the ability to recognize and manipulate phonemes within spoken language. PA tasks require the participant to manipulate the phonemes of spoken words by deleting, segmenting, reordering, or blending syllables. For example, Transposition (or the “Pig Latin” Task) requires participants to say a word by transposing the first sound of the word to the end and then adding “ay.” The Deletion Task asks participants to repeat a nonword and then repeat it again removing a sound.

Phonological Decoding refers to the ability to string together written phonemes and express them as a word. PD tests the reading of phonetically consistent nonwords (e.g., tegwop and linpert). PD tasks are both timed and untimed.

Orthographic Coding refers to the ability to recognize written words as a whole. OC tasks involve the reading of irregular words that violate phoneme-grapheme rules (e.g., yacht) or choosing the correctly spelled word between two different phonetically identical words. The two versions of the choice test (Olson et al. 1985, 1989, 1994) are (1) Orthographic Choice, in which one real word and one nonword are presented (e.g., rime or rhyme), and (2) Homonym Choice, which presents two real words, one of which correctly answers a question (e.g., which is a fruit: pair or pear).

Single-Word Reading tests the ability to read (i.e., sound out) a list of unrelated words that increase in difficulty. These tasks are measured for accuracy, speed, or both (efficiency).

Spelling Ability tests involve the accurate writing of real words, non-words, and irregular words. Individuals with SRD tend to experience spelling difficulties into adulthood, even if other reading related deficits dissipate (Bruck 1990).

In a number of cases (e.g., Grigorenko et al. 2007a), researchers have used the phenotype of reading comprehension (RC); yet, this is not common. Other measures cited in the SRD genetic literature include: Phonological Memory (PM), which is typically tested with Nonword Repetition tasks; short-term memory (STM), which is an indicator of the ability to repeat lists of letters and numbers forwards, and Working Memory (WM), which tests backward repetition or sequencing of letters and numbers (Digit/Letter Span and Letter-Number Sequencing); Rapid Automatized Naming (RAN), which measures the ability to rapidly retrieve sequentially the names of simple stimuli (e.g. letters, numbers, colors, pictures); and tests of Expressive and Receptive Vocabulary (EV and RV, respectively). In addition, the overwhelming majority of research groups utilize indicators of general ability

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(IQ), either for inclusion/exclusion purposes or as continuous indicators of the severity of the deficit. Additional phenotypes used in a minority of publications include Attention Deficit Hyperactivity Disorder (ADHD, which can be captured through categorical or continuous indicators); language ability phenotypes, sampling from all levels and types of language functioning; and even hand preference and head circumference indicators.

Molecular genetics of SRD

At present, SRD twin, family and case–control samples (or DNA collections) have been analyzed within the context of linkage and association studies by several research teams, mainly in North America, Australia, and Europe, having recruited participants who are English (the overwhelming majority) and Non-English (the overwhelming minority) speakers. Yet, despite systematic efforts since the early 1980s and advancements in the technology of genotyping, explorations of the SRD trait while promising remain inconclusive. Putative linkage regions and candidate genes are spread across the genome, supporting the premise that the search for SRD-involved genes is a search for many genetic risk factors of small effect sizes rather than one single risk gene. Attempts at replication have been mixed (Scerri and Schulte-Körne 2010), suggesting the pervasiveness of false positives. These inconsistencies indicate the complex biological machinery contributing to the SRD trait, and point to at least two pervasive methodological problems characteristic of this field. First, samples sizes remain relatively small and may not have enough statistical power to detect or replicate genes with small effect sizes, requiring sample sizes in the thousands for association (McCarthy et al. 2008). For this reason, many SRD molecular-genetic studies often contain uncorrected *P* values, because the results might not be significant after correction for multiple comparisons. Second, there is much heterogeneity within and across samples. The inclusion criteria and phenotypic measures used within studies may be selecting “affected” participants too broadly, resulting in these participants having somewhat divergent cognitive-behavioral profiles. Additionally, different collections define SRD and related phenotypes using different methodologies and thresholds. These sources of heterogeneity, coupled with the obvious impacts of linguistic and environmental differences across samples, are likely to disrupt attempts at replication and prevent the use of meta-analytic techniques to increase the sample size and power. Advancing the genetic study of SRD, most likely, will require larger samples sizes that are collected with increased phenotypic specificity. Yet, genetic linkage studies have converged on nine chromosomal regions for SRD, the so-called dyslexia susceptibility regions DYX1–DYX9 (Grigorenko and Naples 2009; Scerri and Schulte-Körne 2010; Schumacher et al. 2007). Investigations of these candidate regions resulted in the identification of six “recognized” candidate genes (*DYX1C1* at DYX1—15q; *DCDC2* and *KIAA0319* at DYX2—6p; *MRPL19* and *C2ORF3* at DYX3—2p; *ROBO1* at DYX5—3p; and *KIAA0319L* at DYX8—1p). Four of these genes (*DYX1C1*, *ROBO1*, *DCDC2* and *KIAA0319*) demonstrate apparently functional similarity, impacting neuronal migration and guidance (Galaburda et al. 2006). Two recently identified candidate genes (*MRPL19* and *C2ORF3*) have also been found to be highly expressed in the brain (Anthoni et al. 2007), although their function is still unclear. These list so fregions and genes, however, are constantly challenged, as exemplified in this issue as well (Buonincontri et al. 2011; Matsson et al. 2011; Newbury et al. 2011). Yet, the silent convention is to await at least one independent replication of either the region or the gene before adding it to “the list”; thus, every autonomous attempt at replication counts!

Review method

In this manuscript, we present a review of current DNA collections that are being investigated in the field of SRD according to sample design and phenotype assessments. Additionally, we comment on the rate of use, usability, and interpretability of different phenotypes. We performed a literature search for articles using the Ovid search engine.

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Articles were obtained using the key terms: “Dyslexia”, “Reading Disability”, “Reading Ability”, and “Molecular Genetic”, “Association”, “Linkage”, “Haplotype”. Only articles reporting genetic linkage, association, or haplotype analysis for SRD/Dyslexia phenotypes where included. Selection was limited to studies published from 1997 to 2010 that reported primarily on SRD samples. Studies comparing SRD samples with other affected groups (e.g., ADHD or various speech and language impairments) were not included.

Procedure

Seventy-four studies representing 20 DNA collections (or samples of participants who donated DNA) were included in this review (see Table 1). The following information was obtained from each article included in the review: author, year of publication, number of participants, their age, gender, and native tongue, number and type of markers analyzed in the study, and inclusion criteria. Additionally, every *P*-value and LOD score published in each article or in online supplementary materials was recorded with the phenotype it was originated for, along with the statistical analysis, chromosome region, and marker associated with that result. Studies were organized and analyzed according to sample design and phenotypes reported. It is important to stress that the focus of this review is phenotypes, not genetic regions or genetic markers.

Collection summaries

To orient the reader and to provide context for the issue, here we summarize the major collections in the field. The collections are multiple and are presented in alphabetical order (also see Table 1 for more detailed representations of selected collections), unless there is a geographical (i.e., located in the same country or on the same continent) or research (i.e., co-analyzed in some publications) reason for them to be examined in proximity. Of note is that these summaries, although designed to provide a comprehensive overview of the samples used in the field, are not intended to discuss each and every finding presented in the articles, but rather are meant to sample from such findings.

African collections

Afrikaner sample (South Africa)—The Afrikaner Sample consists of all 4th-, 5th-, and 6th-grade students from five Afrikaans-language schools (n = 1,944) located in North West Province of South Africa. The Afrikaner population is an isolated population of migrants of Central and North European descent who exhibit significant genetic homogeneity. The Afrikaans language is most similar to Dutch, but incorporates elements of French, German, Malay, and African languages. Platko et al. (2008) studied the association between SRD phenotypes and markers on chromosome 6p22. The affected status of SRD was assigned to children who scored below the 10th percentile on any of three assessments— PA, PD, or SWR. Twenty-three percent of the sample were identified as cases and the remaining unaffected children were used as controls (genotyped samples were limited to 122 cases and 112 controls due to budgetary limitations). The association analysis of multiallelic markers with the categorical SRD phenotype yielded a significant association *P*-value of .0000139 (P = .00899 after correcting for multiple testing) at marker D6S299.

Tanzanian sample—Another sample adding ethnic diversity to the literature (Grigorenko et al. 2007a, b) assessed 1,476 Tanzanian Swahili-speaking school children tested with a set of reading and spelling tasks at letter, word, and sentence levels. Grade regressed residuals were generated; their distributions were bimodal. Participants were selected if they scored below the upper mode on one of four measures. Among those who met the criterion, there were probands from 84 sibling pairs and four sibling trios; all probands and their siblings were characterized further behaviorally and genotyped. A number of componential

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phenotypes for accuracy and speed were used: (1) PA, (2) PM, (3) RAN, (4) decoding, a composite of real word and nonword reading; and (6) sentence repetition, repeating tongue twisting sentences. Three regions implicated in previous research were analyzed, 2p, 6p, and 15q. The strongest signals were obtained for RAN digit naming errors (LOD = 4.8) and sentence repetition time (LOD = 3.3) on chromosome 6p22. Additionally, chromosome 15q11.2–15q26.3 (harboring, among other genes, *DYX1C1*) displayed suggestive significance for word naming errors (LOD = 2.90) and decoding time (LOD = 3.8).

The Australian sample: Brisbane twin sample

The Brisbane sample was recruited from ongoing adolescent twin studies of melanoma and cognition (Wright and Martin 2004). Participants were mainly recruited from primary and secondary schools in South East Queensland; a smaller portion of the sample was recruited by word of mouth and through the Australian Twin Registry (Hopper 2002). Reading measures were collected from participants from 10 to 25 years of age using a phone-based mailer packet. The original test battery, the CORE battery (Castles and Coltheart 1993), included six measures comprised of reading and spelling tests for nonwords (PD and SA_{NW}), real words (SWR_{RW} and SA_{RW}), and irregular words (SWR_{IW} and SA_{IW}). The participants were mainly Caucasian (98%) and of Anglo-Celtic descent (~82%); the obtained estimates of intellectual ability were comparable to those of the general Queensland population (Luciano et al. 2004). Linkage analysis (Bates et al. 2007) was conducted on a sample of 403 twin families using the CORE battery (Bates et al. 2004), which is an extended version of the reading assessment mentioned above with more difficult items for older participants. The reading and spelling assessments were untimed and presented in mixed order. Univariate multipoint variance components (VC) linkage analysis was conducted for individual measures, yielding several LOD scores of suggestive significance for reading (SWR_{RW}—2.0 at 18p21; PD—1.2 at 1p SWR_{IW}— 2.08 at 4p15.33) and spelling (SA_{RW}—2.18 at 2q22.3 SA_{NW}—2.05 at 7q32 SA_{IW}—2.04 at 6q23.2). While LOD scores for several markers displayed replication of previous findings on chromosomes 1p (Grigorenko et al. 2001), 7q32 (Kaminen et al. 2003), 15q21.1 (Schulte-Körne et al. 1998), 18p21 (Fisher et al. 2002), and Xq27 (de Kovel et al. 2004), none of the novel or replicated markers displayed a score above the accepted threshold of statistical significance (LOD > 3.6). In addition, association studies were carried out (Bates et al. 2008, 2010; Lind et al. 2010; Luciano et al. 2007a, b) using the previously described measures, as well as the composite score of the CORE tests (Lind et al. 2010) and indicators of STM (Bates et al. 2010). The analyses (Bates et al. 2010) conducted on the largest sample (790 families) reported significant *P*-values for the dyslexia susceptibility gene *DYX1C1* (15q21.3) for measures of SWR_{IW} (*P* = .0199 at rs17819126), PD (*P* = .0003 and .0089 at rs17819126 and rs3743204), SA_{IW} (*P* = .0086 at rs17819126), and STM (*P* = .04 at rs685935). Additionally, a recent study (Lind et al. 2010) reported association with a composite phenotype (CORE-PC) for six markers with a maximum *P* = .0016 on candidate gene *DCDC2*. The Brisbane sample is represented in this special issue by Bates et al. (2011).

Canadian collections

The Calgary sample—This sample was recruited through special schools for students with LD. The sample originally consisted of 79 families (Field and Kaplan 1998) and grew to 100 families (Hsiung et al. 2004; Tzenova et al. 2004). Multiplex families were included if the probands were ≥8 years of age and at least two children had a diagnosis of probable or definite dyslexia. Of the 100 families, 96 were of European ancestry. The qualitative phenotype was defined as phonological coding dyslexia (PCD). The tests for PCD included: word attack subtest (PD) from the Woodcock-Johnson Reading Mastery Test (Woodcock 1987) and Woodcock–Johnson Psychoeducational Test (Woodcock and Johnson 1989); PA with the Auditory Analysis Test (Rosner and Simon 1971); spelling (SA) from the Wide

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Range Achievement Test (Jastak and Wilkson 1984); and the RAN numbers task (Denckla and Rudel 1974). Affected status for the PCD phenotype was determined by performance of two or more years behind the age norm on the subtests, with particular weight being given to PD. Self-report histories were also used for parents. Linkage analyses (Hsiung et al. 2004; Petryshen et al. 2000, 2001, 2002; Tzenova et al. 2004) were performed on the Calgary sample looking at the qualitative phenotype PCD and the individual quantitative phenotypes (PD, PA, RAN, and SA). The researchers (Petryshen et al. 2001) reported linkage for the PCD and quantitative phenotypes on chromosome 6q (i.e., LOD scores of 2.82 for PCD, of 3.34 for SA, and of 2.08 for PD). A later linkage study (Petryshen et al. 2002) produced LODs of 2.33 for the PCD phenotype and 3.8 for SA on 2p. A subsequent study (Tzenova et al. 2004) focused on the same phenotypes and a set of markers on chromosome 1p, reporting linkage for the PCD phenotype (LOD = 3.7) and the spelling phenotype (LOD = 4.0). The most recent study from this sample (Hsiung et al. 2004) reported a linkage signal for the PCD phenotype at 11p (LOD = 3.6), but the subsequent association analysis did not localize the signal further.

The Toronto sample—The Toronto sample consists of participants aged 6–16 who were recruited from local schools based on some evidence of reading difficulties. The most recent published report on the sample included 291 families (Couto et al. 2010), mostly described as of European descent or Caucasian Canadians (94%). Parent reports of mental illness or neurological disorders and levels of IQ (<80) were used for child exclusion. Association studies (Couto et al. 2008; Wigg et al. 2004) were conducted using the following measures: SWR and SA from the WRAT-III (Wilkinson 1993); PD and SWR subtests from the WRMT-R (Woodcock 1987); and timed tests of PD and SWR from the TOWRE (Torgesen et al. 1999). Affected status was determined using scores on PD, SWR, and the WRAT-III reading subtest. The qualitative definition of SRD was determined by a score of 1.5 SD below the general population on two out of three reading measures or an average of 1 SD below the mean on all three. This group (Wigg et al. 2004) investigated six polymorphisms of the *EKN1* (also referred to as *DYX1C1*) gene and reported a significant association with one of the investigated SNPs, although the results conflicted with the initial results (Taipale et al. 2003). Subsequently, Couto et al. (2010) investigated 37 genetic markers on 6p (Cope et al. 2005; Deffenbacher et al. 2004; Francks et al. 2004; Meng et al. 2005a; Schumacher et al. 2006a). Evidence of association was observed using the categorical SRD phenotype, as well as PD (TOWRE) and SA (WRAT-3), and a “weak trend” of association for SWR (TOWRE). Of note also is that an association was observed (Couto et al. 2008) with the gene *KIAA0319L* (1p34) and a composite of SWR and PD ($P = .03$) and RAN ($P = .04$). The Toronto sample is represented in this special issue by Elbert et al. (2011).

The Dutch sample

The Dutch Sample includes multiplex SRD families recruited through advertisements in newspapers and magazines. Families were invited if at least two first-degree relatives had a history of reading difficulties. All families reported so far are of European descent. The initial linkage study (de Kovel et al. 2004) reported results from a large multigenerational family of 29 people. Affected status (i.e., SRD or no) was determined using criteria designed by the Dutch Dyslexia Programme (Kuijpers et al. 2003). Specifically, individuals were considered SRD if they scored below the 10th percentile on SWR or PD, or below the 25th percentile on both, or produced a discrepancy score of ≥60% between SWR or PD and the verbal competence test, which assessed the skill of concisely describing the similarity between two words (Uterwijk 2000). In a control group ascertained through Dutch secondary schools, among a total of 560 adolescents, over 20% met the criteria for SRD (as specified above). Using this normative-sample-based criterion, 15 of the 29 family members were classified as individuals with SRD. The whole-genome scan carried out with this

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pedigree and the categorical diagnosis of SRD had a peak multipoint LOD score of 3.68 on Xq27 (de Kovel et al. 2004). Subsequent to these analyses, researchers (de Kovel et al. 2008) investigated 67 markers on chromosomes 1, 2, 3, 4, 6, 7, 8, 9, 11, 15, 18, 21, and X using 108 nuclear families. In this study, in addition to using the categorical phenotype of SRD, linkage results were provided for phenotypes reflective of five quantitative measures: SWR speed and accuracy (SWR_S and SWR_A, respectively); PD; PM; RAN and verbal competence. The peak LOD score for the categorical definition was 2.31 on 1p. Moreover, quantitative phenotypes also displayed suggestive linkage producing an LOD of 1.65 on 1p for the SWR phenotype and an LOD of 1.96 on 2p for the PD phenotype. The RAN phenotype also showed two weak peaks (LOD = 1.5), whose locations correspond to the SWR and PD peaks. The PM phenotype (assessed by a Nonword Repetition task) generated an LOD of 2.28 on 11p; the verbal competence phenotype did not result in any peaks exceeding an LOD of 1.5.

The Finnish collection

The Finnish collection is comprised of families recruited through the children's hospitals in Helsinki and Jyväskylä. Linkage analyses were performed on several families, including a large multiplex family in this collection. The studies used a categorical definition of SRD based on scores on real word and nonword reading fluency and accuracy (SWR_F, SWR_A, and PD_F, PD_A, respectively), real word and nonword spelling (SA_{RW}, SA_{NW}) and/or a history of difficulty for adults with "compensated dyslexia," whose deficits were limited to one reading or spelling measure. Participants were also assessed using PA, RAN, and STM indicators. To exemplify the work on this sample, here we consider the line of research on the *DYX1C1* gene. Specifically, researchers (Nopola-Hemmi et al. 2001) reported linkage for one large four-generation multiplex family ($n = 74$). Affected status was determined if the participant had a positive history and scored at least 1.0 SD below the norm on SWR_F, PD_F or .7 SD below the norm on PD_A and SA_{NW}. SRD diagnosis was established by comparing the participants' reading and spelling scores to a group of age-appropriate controls ($n = 100$). An initial linkage scan was conducted on a subset of the family (21 affected and 14 unaffected) and showed linkage for SRD for a region of chromosome 3 (*P*-value = .0017). A second analysis was performed focusing on region 3p12.1-3q12.3, including the remaining branch of the pedigree, which also generated evidence for linkage (LOD = 3.84). The gene ROBO1 was identified later as a candidate gene for SRD in this region (Hannula-Jouppi et al. 2005). Subsequently (Kaminen et al. 2003), the sample was expanded to 11 families ($n = 97$). Diagnosis of SRD was determined using the previously described Finnish reading and spelling tests. Affected participants had to score 2 years below their age norm and have IQ > 85. Linkage analysis produced two regions of interest with moderately significant LOD scores on chromosomes 2p11 (LOD = 2.55) and 7q32 (LOD = 2.77). A follow-up study (Peyrard-Janvid et al. 2004) using the same sample further explored the chromosome 2p candidate region. Linkage was observed for this region with a peak at D2S2216 (LOD = 3.0) and the size of the candidate region was reduced. Lastly, Taipale et al. (2003) included an association analysis of 8 exons on candidate gene *DYX1C1* using the same inclusion criteria with a sample of 58 cases and 61 controls who were recruited from the Department of Pediatric Neurology at the Hospital for Children and Adolescents, University of Helsinki, and 3 families and 33 couples recruited from the Child Research Centre, Jyväskylä. Significant association was observed on SNPs 3G-A and 1249G-T in an initial case–control sample (*P*-values of .006 and .02, respectively); an independent case–control replication sample yielded *P*-values of .02 and .1 (Taipale et al. 2003). The Finnish sample is represented in this special issue by Matsson et al. (2011).

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The German collections

The Marburg–Wurzburg sample[3]—One German sample includes families with at least two siblings with SRD recruited through clinical referrals from Philipps-University in Marburg and Julius-Maximilian University in Wurzburg (Schulte-Körne et al. 1996). Probands were ascertained if they had a diagnosis of SRD and a history of spelling difficulty. Children were labeled SRD if they had a spelling score ≥1 SD below their expected score based on IQ. Additionally, adults who were labeled as "affected" were required to profess a history of significant spelling difficulty. Initial linkage studies with this German sample tested seven multiplex families using the IQ spelling discrepancy score (DIS). Modest evidence of linkage with a LOD of 1.78 in chromosome 15q21 was found, but significance for chromosome 6 was not achieved (Nöthen et al. 1999; Schulte-Körne et al. 1998). In more recent years the sample has expanded. The most recent linkage analyses included the discrepancy phenotype in addition to five component phenotypes: SWR efficiency (SWR_E); PD efficiency PD_E; PA (three tasks—segmentation, deletion, and reversal vs. four tasks—segmentation, reversal, binding, and reversal were used to define this phenotype for children at or above grade 5, respectively); OC using the pseudohomophone test (OC_{PH}), and RAN (colors, objects, letters, and numbers). Individuals with ADHD were excluded from the sample using a standardized clinical interview. A number of linkage and association studies have been performed with this sample. Schumacher et al. (2006b) performed a linkage analysis of chromosome 18p11-q12 with 82 families, but no linkage peaks exceeded a LOD > .6 for any phenotypes. Subsequently, these researchers (Schumacher et al. 2008) searched for linkage on 15q using the same sample and phenotypes. Modest evidence of linkage was observed using the SRD discrepancy phenotype (LOD = 1.2 and 1.3 for markers D15S182 and D15S143, respectively). No evidence of linkage was observed for the componential phenotypes. Several association studies have also been conducted using the German sample and the discrepancy and component phenotypes described above. Specifically, researchers (Schumacher et al. 2006a) performed an association analysis for the *DCDC2* gene on 6p and a number of reading-related phenotypes. The initial sample used in the study consisted of 137 family triads and a replication sample of 239 triads tested in full and broken down into subsets by severity. No evidence of association was observed for any of the component measures. However, significant association was observed for the spelling discrepancy phenotype in both the initial and replication sample. An association study of *KIAA0139* and *DCDC2* with 244 families (where the probands met the criterion of 2 SD discrepancy score between SA and IQ) utilized the qualitative phenotype DIS and SWR, PD, and SA (Ludwig et al. 2008a, b). No association was observed for *KIAA0319*, but an interaction analysis between SNPs of the two genes yielded a modest *P*-value of .0351. The subsequent association study (Schumacher et al. 2008) of 82 families did achieve significant association for the SWR component phenotype (most significant; $P = .0003$ at 15q) and the discrepancy phenotype. Yet, further investigations of the association between *DCDC2* and SRD-related phenotypes in 396 family trios failed to find any evidence of association with the previous phenotypes (Ludwig et al. 2008b). The sample was later evaluated for an association between the STM phenotype (assessed by the digit-span task) on *GRIN2B* (12P), reaching a significant *P*-value = .0243 (Ludwig et al. 2010). The increasing severity criterion for affected status was also applied to this study, but did not improve association significance between variants of *GRIN2B* and the reading-related behavior phenotype STM. A sample of 366 family trios was used in the association study with and variants in *DYX1C1* and all previously mentioned phenotypes–DIS, SWR, PA, PD, OC, RAN, and STM (Dahdouh et al. 2009). Significant association was observed using the DIS categorical phenotype ($P = .036$). The most significant *P*-value (.006) was observed in the female subset of the sample. STM was the

[3]Of note: this sample has been used jointly with the Finnish Sample (e.g., Anthoni et al. 2007).

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only other phenotype to show evidence of association ($P = .011$). This German sample is represented in this special issue by Czamara et al. (2011).

The Leipzig sample—An independent German sample (Wilcke et al. 2009) includes 72 3rd- and 4th-grade children with SRD who were recruited through schools specializing in education for children with reading difficulties. Children with math and memory deficits were removed from this sample, as well as children with ADHD or IQ < 85. Reading ability was assessed using a standardized German battery, which included word level decoding, sentence RC, and auditive understanding (Marx 1998). An IQ reading performance discrepancy score of 1.5 SD was applied to determine the SRD status. The subgroup was determined for cases with a discrepancy score of 1.5 SD between IQ and the indicator of PD (dysphonetic phenotype). A case–control association study of gene *DCDC2* on chromosome 6p was conducted using the abovementioned phenotypes for the affected samples and 184 controls. Significant association was achieved ($P < .001$), which replicates the association with the *DCDC2* deletion reported in the CLDRC sample (Meng et al. 2005b). The association was not observed in the dysphonetic subgroup, but was significant for nondysphonetic cases ($P < .005$).

The Indian sample—One of the few non-European samples included 51 Indian children with SRD recruited from special schools for LD at Karnataka state (Saviour et al. 2008). Probands had reading and spelling scores two grades behind Indian grade standards. Additional clinical assessment and school histories were used to verify the findings. The sample was analyzed for association between the SRD status and markers in *DYX1C*. No significant evidence of association was observed in this sample. This sample is represented in this special issue by Venkatesh et al. (2011).

Italian collections

The Bosisio Parini sample—Four studies with this Italian sample have investigated genetic risk variants in four dopamine-related genes (Marino et al. 2003) and on 15q (Marino et al. 2004) and *DYX1C1* (Marino et al. 2005). In the initial studies (Marino et al. 2003, 2004), children were recruited from the Department of Child Psychiatry and Rehabilitation Centre at the Eugenio Medea Institute, Bosisio Parini, Italy. The researchers administered a number of assessments—text reading accuracy and fluency (TR_A and TR_F), SWR_A and SWR_F, and PD_A and PD_F—and compared these results to that of a normative sample. Children were selected if: (1) they scored 2 SD below grade norm on TR_A and TR_F; or, (2) they scored1.5 SD below grade norm on either TR_A or TR_F, and 2 SD below the norm on one other measure (SWR_A, SWR_F, PD_A or PD_F). No indication of association was obtained with the dopamine-related genes (*DRD2–4* and *DAT1*). The exploration of the 15q region was more promising: no single-marker associations were found, but a three-marker haplotype (D15S214/D15S508/D15S182) captured a signal at $P = .005$. The sample was then expanded to 158 probands (Marino et al. 2005) and component phenotypes (PD, OC, SWR, SA_W and SA_{PW}, for spelling of words and pseudowords, respectively) were analyzed. Once again, there was no indication of an association between the *DYX1C1* gene markers with either categorical or componential phenotypes. The third publication expanded the sample to 212 probands (Marino et al. 2007); the inclusion criteria was reduced and set at 1 SD below grade norm on reading measures. The Digit Letter Span task was added to the assessment battery and produced the only significant association (Letter Backwards) at $P < .0011$. This Italian sample is represented in this special issue by Marino et al. (2011).

The Naples sample—A second Italian sample was recruited from the Department of Pediatrics and Child Neuropsychiatry of Naples, Catania, and Messina (Bellini et al. 2005). Probands were selected for inclusion at a reading performance of 2 SD below the age/grade

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norm on TR, SWR, and PD tasks. A case–control association study was carried out with the 57 probands and 96 controls. No association was observed between the SRD-related phenotypes and variants in the *DYX1C1* gene.

The Norwegian extended family

The Norwegian Family sample consists of a large extended family (n = 36), ascertained using a series of computerized assessments. The test battery included nine assessments: SWR accuracy, SWR_A; SWR fluency, SWR_F; timed SWR_A in which the word appears on the screen for 100 ms; timed SWR_F; PD accuracy, PD_A; timed PD_A; PA assessed by a phoneme blending task using both real-words and non-words; and spelling real words and irregular words (SAR_W and SAR_{IW}, respectively). Cutoff points were determined for each of the tests based on population norms, family distribution, and family histories of reading difficulties. Family members were considered affected if they scored below the cutoff on two of the nine tests, as long as one of the tests was a PD task. The cutoff points used were based on adult data because there were too few children to anchor the results; consequently, there was potential for bias in interpreting the child sample. Linkage analysis was carried out using three phenotyping models to determine the status of SRD: Model (1) included participants with test scores indicative of reading problems; model (2) included both control and SRD cases with both test scores indicative of reading problems and history of SRD; and model (3) the same as model (1) but excluded children under the age of 20. Significant LOD scores were observed for models (1) (LOD = 3.5) and (3) (LOD = 4.3) on chromosome 2p15–16. Additionally, suggestive significance (LOD = 2.93) was observed using model (2) in the same genetic region.

The UK collections

Avon longitudinal study of parents and children, ALSPAC (UK)—The ALSPAC sample consisted of families of European descent in South West England (Golding et al. 2001). The sample was originally ascertained to represent the general population and study the genetic and environmental influences of health and development through pregnancy and childhood. Starting at birth, children were annually assessed for a variety of developmental traits, which included reading ability, recorded at ages 7 and 9. Overall 5,300–7,200 (Paracchini et al. 2008) children were included for each phenotypic indicator. The assessments included two dichotomous phenotypes: (1) parent-report of reading difficulties at age 7 leading to school intervention; and (2) a below target level score on a reading and RC test from a school-based reading Statutory Assessment Test. Moreover, continuous measures included: reading single words (SWR) from the Wechsler Objective Reading Dimensions test (Rust et al. 1993); spelling (SA) assessed with 15 real words; PA assessed with the Phoneme Deletion Task (Rosner and Simon 1971); and SWR and PD accuracy (Neale 1997). The analyses were conducted for the *KIAA0319* gene (Paracchini et al. 2008). Separate analyses were carried out for the full sample with and without adjustment for IQ, and an IQ cut-off score of >90. Additionally, severity was compared using a range of high-low cutoffs at 25–75, 10–90, and 5–95%. Significant association was observed for SWR and SA indicators for all analyses, and PD for the >90 IQ subset. Replicating previous findings (Francks et al. 2004), association was most significant for the >90 IQ subset with significant P-values of .001 (SWR), .008 (SA), and .030 (PD).

The Cardiff sample (UK)—This UK sample was collected from educational authorities in Southern Wales and English schools that specialize in educating students with reading difficulties. The inclusion criteria for the study was at least 2.5 years discrepancy between chronological and reading age using the Neale Analysis of Reading Ability (Neale 1989) and normal (>85) IQ score. In their first publication (Morris et al. 2000), researchers performed an association analysis to further explore chromosome 15q using a two-stage

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approach with one group of 101 parent-proband trios (stage 1) and a second group of 77 trios (stage 2). At stage 1, eight microsatellite markers were investigated producing significant associations for the categorical SRD phenotype, including a three-marker haplotype D15S146/D15S214/ D15S994 ($P < .001$), whose association with the SRD phenotype was re-established at stage 2 ($P = .0091$). A second set of association analyses using the same two-stage design (Turic et al. 2003) was carried out with a set of markers on 6p using the previous samples, methods, and additional reading-related componential measures. The nine reading related component phenotypes included: PA—Phoneme Deletion (Rosner and Simon 1971) and Rhyme Oddity (Bowey and Patel 1988); PD; PM; OC accuracy and latency (or speed) (OC_A and OC_L, respectively), assessed by the Pseudohomophone Judgment Task (Olson et al. 1994); RAN (Objects and Digits); SWR; SA; and expressive vocabulary, EV assessed by the WISC-III (Wechsler 1992). Significant association was observed for two markers during the single-marker analyses, but failed in the second stage replication. The researchers, however, were able to establish at stage 1 and replicate at stage 2 findings on a two-marker haplotype. Additionally, significant association ($P < .005$) was observed and replicated for the three marker haplotype D6S109/422/1665 with 6 component phenotypes including SWR, SA, PA, PD, OC_A, and RAN. A subsequent study (Morris et al. 2004) used a case–control design incorporating the probands from the previous sample as well as additional affected individuals who met the inclusion criteria. Specifically, 164 SRD probands and 174 controls (i.e., matched SRD-free individuals) from the same schools were analyzed for association with two candidate genes (*PLCB2* and *PLA2G4B*) located on 15q. Moderate association was observed at a marker within the *PLCB2* gene using the categorical SRD phenotype in the case–control sample, but was not replicated using the family trio sample. A follow-up study (Cope et al. 2004) failed to find association with the candidate gene *DXY1C1*. Additionally, Cope et al. (Cope et al. 2005) used the same design with an expanded sample (223 cases and 273 controls) to perform an association analysis of the *KIAA0319* and nearby genes on 6p. Significant association was observed and replicated for a two-marker haplotype rs4504469/rs6935076 by the case–control ($P = .00001$) and family trio samples ($P = .02$). Harold et al. (2006) continued the analyses of the genes on the 6p22.2 region using the Oxford and Cardiff samples both independently and pooled. The association analysis confirmed previous linkage and association studies for the *KIAA319* and *DCDC2* genes with significant results using component measures described previously.

The Oxford sample (UK)—The Oxford sample[4] consists of families recruited through the dyslexia clinic at the Royal Berkshire Hospital in Reading, United Kingdom. Probands were selected on the basis of a discrepancy greater than 2 SD between their reading score on the British Ability Scale (BAS) and verbal or nonverbal reasoning. Families were included if at least one other sibling of the proband had a history of reading difficulty. All participants were of European descent. Studies using the Oxford sample have reported linkage and association using several different reading related phenotypes. An initial linkage study (Fisher et al. 1999) included 82 families using the SWR and IQ discrepancy (DFS) phenotype. OC was assessed with an irregular word reading test (e.g. *meringue*); PD–using a nonword reading task. Lastly, a composite score was produced using the age-adjusted scores from OC and PD. Significant linkage was reported for the OC and PD phenotypes. This sample has been published on extensively (Fisher et al. 1999,2002;Francks et al. 2002;2004;Marlow et al. 2001,2003;Scerri et al. 2004). The more recent studies included SWR, SA, PA, PD, and two OC assessments–Orthographic Choice, OC_{OC}, and Irregular

[4]Of note is that there are publications that utilize multiple samples, e.g., the Oxford sample and the CLRDC. For example, Fisher et al. (2002) conducted independent genome-wide linkage scans of 401 microsatellite markers with the Oxford and CLDRC samples, followed by a linkage analysis of five markers on chromosome 18p11.2 with the Oxford sample. A follow-up study by Francks et al. (2004) also used the CLDRC and Oxford samples.

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Word Reading, OC_{IW} (Dennis et al. 2009;Francks et al. 2004;Scerri et al. 2004). Additionally, the sample has been expanded to now include 264 families (1,153 individuals) with probands who scored ≥1 SD below the age norm on SWR ability in the presence of a minimum IQ score of 90 (Dennis et al. 2009;Francks et al. 2004;Scerri et al. 2004). For example, the most recent linkage analysis reported no significant linkage for the six phenotypes in the region harboring the *DX1C1* gene (Scerri et al. 2004). The only reported value was a LOD score of 1.0 for the PD phenotype (in the D5S132-D15S143 region). The authors also reported association findings with somewhat significant *P*-values for OC_{OC} (*P* = .0212) and SWR (*P* = .0642). The most recent quantitative trait association analysis, using the previously mentioned phenotypes, was carried out in the Oxford sample for the *KIAA0319* gene on 6p (Dennis et al. 2009). Significant association was observed for OC_{IW} (*P* = .0025), OC_{OC} (*P* = .0044), and SA (*P* = .0084). A subset of "severe" probands (*n* = 126) was differentiated from the rest of the sample based on the PD and OC_{IW} composite score of >.5 SD below group mean and IQ > 90. In this subset, significant association was reported for OC_{IW} (*P* = .0003), OC_{OC} (*P* = .0001), PD (*P* = .0362), SWP (*P* = .0002), and SA (*P* = .0018). The Oxford sample is represented in this special issue by Newbury et al. (2011).

The twins early development study (TEDS)—Meaburn et al. (2008) performed a genome-wide association scan using a set of 100 K SNPs in a sample of 5,760 high and low ability readers from the TEDS (Oliver and Plomin 2007). The TEDS sample is comprised of twins recruited from Wales and England for longitudinal genetic analyses of behavioral problems in children. At age seven, the TEDS participants were administered SWR efficiency and PD efficiency tests from the TOWRE (Torgesen et al. 1999) and a modified IQ test for phone-based administration (Wechsler 1992). Additionally, a teacher, using a standardized assessment scale based on the UK National Curriculum Criteria, evaluated each participant's reading performance. High and low readers were determined using a composite score based on the reading assessments and teacher assessment, which are correlated at *r* = .69 (Dale et al. 2005). The initial analysis of 107,116 SNPs was conducted with the upper and lower quartiles of the distribution based on the composite reading scores (747 high ability and 755 low ability). 75 SNPs were nominated and analyzed in an independent sample scoring in the upper and lower 10th percentile on the reading composite score (*n* = 850; 425 high- and 425 low-scoring participants). Lastly, the SNPs were narrowed down to 23 and analyzed for association in the entire sample of participants (*n* = 4,258). 10 SNP's were significantly associated with difference in reading indicators, reaching a peak *P*-value of .003 on chromosome 14q24.2. All 10 SNPs reside in novel regions that have never been underscored as "interesting" in previous studies of SRD and reading-related regions. The TEDS sample is represented in this special issue by Docherty et al. (2011).

The USA samples

The Colorado Learning Disabilities Research Center (CLDRC) Collection—The Colorado Learning Disability Research Center (CLDRC) collected DNA from twin pairs recruited from Colorado school districts. Families with at least one twin having a school history of reading difficulties were included; both twins and other siblings were ascertained, when possible (DeFries et al. 1997). Participants underwent an extensive evaluation with a test battery made up of subtests from the Wechsler Intelligence Scales (Wechsler 1974, 1981), the Peabody Individual Achievement Test, PIAT (Dunn and Markwardt 1970) and individual measures of SWR, OC, PD, and PA (Olson et al. 1994). Results from linkage and association analyses have been reported using the discriminate function score (DFS) from the PIAT reading recognition, RC, and spelling subtests (Cardon et al. 1994; Deffenbacher et al. 2004; Kaplan et al. 2002; Meng et al. 2005a, b) and 10 other composite and

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componential phenotypes (Gayán et al. 1999; Kaplan et al. 2002; Meng et al. 2005a, b). These phenotypes included: the SWR accuracy (SWR_A), fluency (SWR_F) and the composite (averaged Z-scores of the former, SWR_C) phenotypes; the OC as assessed by the Orthographic Choice task (OC_{OC}) and by the Homonym Choice task (OC_{HC}), and as represented by a composite of the two tasks (OC_C); the PD phenotype [a composite score of non-word reading accuracy and fluency, recorded with the median correct reaction time, as in Olson et al. (1994)]; and the PA phenotype as assessed with the Phoneme Transposition Task (PA_{PT}), the Phoneme Deletion Task (PA_{PD}), and the tasks' composite (PA_C).

This group (Deffenbacher et al. 2004) reported evidence for linkage and association on 6p in the largest sample in the US literature today (i.e., 1,559 participants from 349 families); this sample included families from previous studies (Cardon et al. 1994, 1995; Gayán et al. 1999; Kaplan et al. 2002). The five phenotypes tested were DFS, PD, PA, OC, and SWR. Significant *P*-values were reported for all 5 phenotypes both for linkage and association analyses. OC showed the lowest (.0004) *P*-value for linkage and SWR—the lower (.001) *P*-value for association tests. Subsequent analyses of the 6p region resulted in the identification of two candidate genes for SRD, *DCDC2*—in the CLDRC sample only (Meng et al. 2005b) and *KIAA0319*—both in the CLDRC and the Oxford, see below, samples (Francks et al. 2004). A study of the *EKN1* (*DYX1C1*) gene with the previously described phenotypes failed to show the association (Meng et al. 2005a). The CLDRC sample is represented in this special issue by Bidwell et al. (2011).

The Orton sample—The probands in this sample were ascertained from a set of 115 adults who had previously been assessed with standardized IQ and reading related measures including: two PA measures (Lindamood and Lindamood 1972; Rosner 1979), two measures of PD and two of SWR (Richardson and DiBenedetto 1985; Woodcock and Johnson 1977), and two measures of RAN, Objects and Colors (Denckla and Rudel 1976). Probands were included if they scored below the 10th percentile on at least one indicator of reading-related measures or below the 25th percentile on two tests of a component phenotype and were married with children, having at least three first- or second- degree relatives. Participants were excluded if there was a history of neurological impairment, mental retardation, or major sensory disability. Four linkage analysis studies have been reported (Grigorenko et al. 1997, 2000, 2001, 2003) using the Orton family sample. The initial study (Grigorenko et al. 1997) assessed six multiplex families ($n = 94$) using the four component phenotypes: PA, PD, RAN, SWR, and a categorical phenotype (SRD) based on a discrepancy between indicators of vocabulary and reading performance. Linkage signals were obtained on chromosomes 6p and 15q. Follow-up studies (Grigorenko et al. 2000, 2003) added two more families to the sample and focused on the 6p region. Seven phenotypes were investigated, including SA, Vocabulary, and Life-Long Diagnosis of SRD. The most significant results were achieved using the PA and SWR phenotypes. Finally, a separate study investigated linkage to the 1p region (Grigorenko et al. 2001). The phenotypes that revealed linkage signals were SWR and RAN.

The Seattle sample—The Seattle sample includes families with school-age children with SRD who were referred to the study by parents and education specialists. The inclusion criteria was a verbal IQ of at least 90, a score below the population mean on one of ten measures (including SWR, PD, SA, TR_A and TR_F, and handwriting automaticity), and a discrepancy of 1 SD below IQ score on one of the ten measures. The initial study (Chapman et al. 2004) of this sample explored linkage to previously implicated regions 2p, 6p, 15q, and 18p. One hundred and eleven families participated in this study. The phenotypes used for this analysis were PD efficiency (PD_E) and SWR_A. Moderately significant linkage (LOD = 2.3) was observed for SWR on chromosome 6p. A follow-up genome-wide linkage scan (Raskind et al. 2005) of 108 markers compared tests of PD accuracy (PD_A), PD efficiency

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(PD_E), and PD_E adjusted for PD_A. The strongest single marker signal was achieved with PD_E (LOD = 3.0). A subsequent study (Igo et al. 2006) used the same sample and three phenotypes, SWR_A, SWR_E, and SWR_E adjusted SWR_A. Again, SWR_E produced stronger results (LOD = 2.9, 13q), with additional peaks for SWR_A on chromosomes 2 and 15. Case–control association studies were performed on the Seattle sample for candidate genes *DYX1C1*, *KIAA0319* and *DCDC2* (Brkanac et al. 2007). An expanded sample of 191 probands and their families were selected using the same criteria mentioned above. The componential phenotypes included the SWR and PD phenotypes (see above), SA, and verbal IQ (Wechsler 1991). A weak trend towards association was observed for *DYX1C1* for the qualitative phenotype. Researchers from this group (Brkanac et al. 2008) also performed a genome scan of PM (assessed by nonword repetition). Three analyses were conducted using an initial sample (DS-1; 51 probands), replication sample (DS-2; 93 probands), and combined sample (DS-C). Linkage for DS-1 was observed (LOD = 3.2) on chromosome 17; suggestive linkage was observed on chromosome 4 (LOD = 2.4) and chromosome 12 (LOD = 2.0). DS-2 also identified regions with evidence of linkage on 8p (LOD = 2.9), 20p (LOD = 2.6), and 7q (LOD = 2.4). DS-C multipoint linkage analysis yielded a LOD score of 2.15 on chromosome 4. The Seattle sample is represented in this special issue by Rubenstein et al. (2011).

Results and discussion

A number of observations have emerged as a result of our review. These observations are presented and discussed below.

Proband selection

Several sample design differences were observed across each collection including: recruitment, inclusion criteria (see Tables 1 and 2), and phenotypic measures. Participants are generally recruited in three ways: clinical referrals from diagnostic/treatment facilities, typical and special education schools, and representative samples. Inclusion/ exclusion criteria typically remove individuals with psychiatric or neurological disorders and visual or hearing impairment. Studies also differ in the inclusion/exclusion of individuals with comorbid diagnoses of attention deficit-hyperactivity disorder (ADHD) and the IQ cut-off, which ranged from 80 to 90.

SRD studies generally use five methods for establishing affected/unaffected status. First, case histories have been used mainly in large multiplex families to identify compensated individuals with SRD or confirm test scores. Second, tests from standardized diagnostic batteries for reading ability such as the Cambridge Contextual Reading Test (Nelson and Willison 1991) and the Neale Analysis of Reading Ability (Neale 1989) have been used mostly in UK studies to select probands who score >2 SD below their peers or >2–2.5 years behind their chronological age. Third, IQ discrepancy score ranging from a 1 to 2 SD difference between reading measures and IQ has been used. Moreover, composite scores from experimental test batteries of multiple reading related measures have been used to establish both summative quantitative and qualitative phenotypes. Lastly, various combinatory criteria (e.g., scores below the population mean on one or more component measures of a particular test battery or multiple test batteries) have been utilized. The deficit severity used for selection (see ‘SRD Affected Status’ in Table 2) ranged from 1 to 2.5 SD below the “population norms,” however defined. Notably, the more severe phenotypes tend to produce more significant results despite reduction in sample size (e.g., Anthoni et al. 2007; Deffenbacher et al. 2004; Dennis et al. 2009; Harold et al. 2006; Schumacher et al. 2006a), although the replicability and nature of this tendency is unclear.

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Sample collection is challenging, particularly when recruiting families. As a result, convenience often plays a major role in the selection and recruitment of probands and their families, thus, inevitably, contributing to the heterogeneity of the resulting samples. Participants are recruited through Clinical Referral, special education programs, or the general population. Individuals seeking clinical assessment are likely more economically advantaged and have resources for remedial training, changing the child's performance. Furthermore, public schools may disproportionately assign individuals to special education according to gender, behavior, or deficit profile, while private schools for individuals with SRD may introduce other biases in proband selection.

Age-ranges vary substantially across studies, and probands may be children or young adults. As a result, different measures are used to test the same construct for each age group. Since the development of phonological processing changes over time with individual variation, cutoffs for different age groups may not identify individuals with the same level of deficit. Consequently, such age differences both in the selection and in maturation might result in the lack of replicability of the findings (Lasky-Su et al. 2008).

Componential phenotypes

Beginning with Grigorenko et al. (1997), componential aspects of the SRD phenotypes have been analyzed to clarify the relationship between genetic risk factors and SRD. Today, the overwhelming majority of studies report values for at least one componential measure—SWR, PD, PA, OC, or SA. Additional indicators such as RAN, PM, WM, and STM have also been reported, but the number of studies that utilize them and their relative placement with regard to the significance of findings is limited (see Table 1). Figures 1 and 2 show the "impact profiles" of each of the six *primadonna* phenotypes of SRD in the context of linkage and associations studies.

It is important to make a few comments about the usage of componential phenotypes in molecular-genetic studies of SRD. First, although many studies assess similar (or the same) cognitive abilities, different tests and subtests are used to measure the same reported phenotypes. For example, PA may be measured with phoneme-deletion (Cope et al. 2005; Meng et al. 2005b; Paracchini et al. 2008), spoonerisms (Chapman et al. 2004), rhyme oddity (Turic et al. 2003), phoneme transposition (Kaplan et al. 2002), individually, or composites of several measures (Deffenbacher et al. 2004; Fisher et al. 2002; Francks et al. 2002; Grigorenko et al. 1997; Wigg et al. 2004). Although all PA measures involve phoneme manipulation and are highly correlated (Anothny and Lonigan 2004), moleculargenetic findings are not necessarily consistent across all measures of PA. It appears that PA and PD were not consistently successful across multiple studies presented here. Multiple factors can contribute to these inconsistencies. First, it is likely that the wide age ranges across studies is one of the sources of such variations. Phonological skills greatly influence acquisition at the beginning stages of reading development (Vellutino et al. 2004; Wagner et al. 1997). Thus, Paracchini et al. (2008) reported success using the PA phenotype in a large case–control study in which the children were tested at age 7. Most studies generally recruit participants in "late" primary-school and middle-school grades. Additionally, Paracchini et al. (2008) used the Phoneme-Deletion task for PA, which is one of the more simple PA tasks. In general, other PA tasks like "spoonerisms" require a heavier load of executive functioning (Ramus and Szenkovits 2008). Consequently, the usage of this phenotype can tap not only the genetic load for PA, but also the genetic load for working/STM.

This was also the case for OC, which was measured with different tasks including: Reading lists of irregular words, such as *yacht* (Bates et al. 2007, 2008, 2010; Fisher et al. 1999, 2002); Homonym Choice (Meng et al. 2005b); Orthographic Choice (Francks et al. 2004;

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Kaplan et al. 2002; Scerri et al. 2004); or a composite of the two tasks (Deffenbacher et al. 2004; Gayán et al. 1999). Yet, across English-speaking populations, OC indicators demonstrated the most consistent trends towards significance. The success of these measures in differentiating affected individuals may result from the accuracy of administration. Irregular word reading is a recognition task in which correct and incorrect answers should be obvious to the administrator, unlike non-word reading tasks, in which more subtle errors need to be detected. Furthermore, the OC-choice tasks also involve simple administration with two possible answers. SWR was also successful across multiple samples. Interestingly, SA, although correlated with OC, showed the smallest number of consistently replicable significant results despite being widely used and including regular words, non-words, and irregular words separately. This is not entirely surprising since the acquisition of skilled reading and spelling can diverge. Skilled readers can still present spelling difficulties (Frith 1980). As a result, spelling tests might not be preferable, except in the cases of transparent orthographies in which phonological tests are not able to differentiate children.

Additionally, often the same phenotypes are assessed in two dimensions, accuracy and speed. This is the same for many studies in which both SWR and PD are captured. Yet, there is some evidence that different dimensions of the same psychological process might generate rather different phenotypes. Thus, in a quantitative-genetic study, Chapman et al. (2003) compared two measures of PD: (1) a PD accuracy test—the Word Attack subtest from WRMT-R (Woodcock 1987); and (2) a PD efficiency test–TOWRE (Torgesen et al. 1999). The results indicated that the two measures demonstrate different models of inheritance and are associated with different amounts of explained genetic variance. Further utilization of these phenotypes in molecular-genetic research (Igo et al. 2006; Raskind et al. 2005) supported this conclusion by establishing differential linkage profiles with the accuracy and efficiency measures of SWR and PD, with efficiency (i.e., combined) scores producing higher significance than either accuracy or speed alone.

Of note also is that indicators of STM and RAN are underrepresented in the literature. The incorporation of these and other distinct quantitative measures might develop more specific phenotypes, thereby decreasing heterogeneity and clarifying the distinctions between SRD subtypes.

Thus, the relationship between individual componential phenotypes of SRD and genetic risk variants continues to be a conundrum. This riddle can have multiple solutions, such as pleiotropic gene effects, phenotype heterogeneity across samples and languages, differential age and maturation effects, or measurement error.

Phenotyping in different languages

Of note is that, so far, more than 2/3 of published moleculargenetic studies of SRD report on English-speaking samples. The majority of the remaining studies utilize samples with European languages (Dutch, Finnish, German, Italian, Norwegian) and report mainly qualitative phenotypes (~75%), as opposed to English-speaking samples that report ~78% component results (Fig. 3). Comparing results of genetic studies of SRD when they are conducted in different languages is challenging because the orthographic transparency of the language will change children's approaches to literacy acquisition and performance on component measures (Frost et al. 1987). Languages with transparent orthographies are defined by consistent grapheme-phoneme relationships and allow children to use reliable PD strategies when learning to read. English, however, is a more opaque language than, for example, Finnish, German or Italian, and students adopt more whole-word strategies to compensate for the inconsistent grapheme-phoneme relationships (Goswami et al. 2003). For example, German-speaking children do not struggle with mapping inconsistencies as much as English-speaking children do (Landerl et al. 1997), so that PA and PD deficits tend

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not to be central to SRD manifestation in German (Wimmer 1996). Thus, the assessment profile of SRD and, correspondingly, its linkage/association profile will differ in more or less transparent orthographies requiring, perhaps, different inclusion/exclusion and SRD definition criteria.

At this point, there is very limited ethnic diversity in the SRD samples. Until recently (Grigorenko et al. 2007b; Saviour et al. 2008), samples utilized in molecular-genetic research have been comprised almost entirely of individuals of Anglo-European descent. Limiting ethnic diversity within a study can improve power and reduce error caused by population stratification (i.e., the different prevalence rates of risk alleles across ethnic ancestries). Yet, association studies with careful case–control matching or family design can accommodate diversity. A serious limitation for including diverse nations in molecular-genetic studies of SRD is the lack of standardized measures in countries outside Western Europe and North America. As a result, less standardized and more diverse inclusion methods are used that are not as representative of the field. Furthermore, cross-cultural conceptions of LD differ around the world, making the utilization of unified methods of diagnosis and inclusion/exclusion criteria difficult.

It has been shown that investigations of different ethnic populations can produce novel risk alleles that are unique or more prevalent in a specific ethnic group (McCarthy et al. 2008). Diverse samples also test the generalizability of findings across different populations. Now, statistical approaches for combating population stratification are present in multitudes, so including representatives of diverse populations, whether within the same sample by utilizing careful case–control matching or family designs or across multiple samples from diverse ethnic and populations backgrounds, needs to be a priority.

In conclusion, the landscape of molecular-genetic studies of SRD and other LD is complex (Miller and McCardle 2011). Although no “definitive” findings pertaining to the genetic bases of SRD have been obtained, there has been a tremendous amount of progress toward understanding these bases. And there is only one possible way to decipher them—to continue studying them, taking into account the intricacy and complexity of the phenotypes they control.

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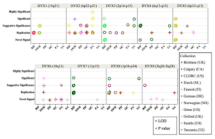

Fig. 1.

Positive results from Linkage analysis of the nine Dyslexia susceptibility regions (DYX1–9) are displayed. Novel signal: First reported positive results for a region with a LOD ≥ 1.2 or *P* value ≥.01. Replication: LOD ≥ 1.2 or *P* value ≥.01 for studies replicating a region. Suggestive significance: LOD ≥ 2.2 or *P* value ≥.00022. Significant: LOD ≥ 3.6 or *P* value ≥.000074. Highly significant: LOD ≥ 5.4 or *P* value ≥.0000003 (Color figure online)

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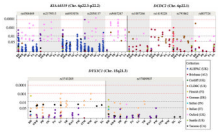

Fig. 2.

Charts display *P* values from association tests of replicated SNPs from three SRD candidate genes using different phenotypes. The *X*-axis indicates the phenotypes used in the analysis. The *Y*-axis presents *P*-values (Color figure online)

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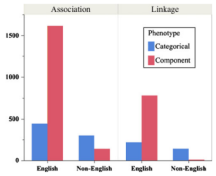

Fig. 3.

Comparison of linkage and association values reported in the literature for each phenotype and genetic marker. English speaking samples are overrepresented in the literature and characterized primarily with componential phenotypes. Non-English speaking samples are mainly characterized with categorical phenotypes (Color figure online)

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Table 1

Description of the studies reporting linkage and association for reading related phenotypes

Collection	Publication	Samples	DXY#	Location (*Gene*)	Analysis	Markers	Phenotype[a,b]								
							RD	SWR	PD	oc	PA	SA	RAN	PM	STM/ WM
Afnikaner (South Africa)	Platko et al. (2008)	122 Cases and 112 Controls		Replication	Association	68	3								
ALSPAC (Uk)	Paracchini et al. (2008)	~ 5,300 to 7,200 Children	2	6p22 (*KIAA0319*)	Association	4	3	1	1		2	2			
Brisbane (Australia)	Bates et al. (2007)	403 Nuclear Families	(8, 9)[a]	Genome Scan	Linkage	796		(2.0)	(1.2)	(2.1)		(2.2)			
	Luciano et al. (2007b)[c]	440 Nuclear Families	2	6p22 (*KIAA0319*)	Association	10	2								
	Luciano et al. (2007a)[c]	248 Nuclear Families	2	6p23, 12p31, 14q32	Association	3	X	X							
					Linkage	3	X	X							
	Bates et al. (2008)[c]	789 Nuclear Families		1q31, 8q, 9q, 17q	Association	4		X	X	X				X	X
	Bates et al. (2010)	790 Nuclear Families	1	15q21 (*DYX1C1*)	Association	13		X	3	1		2			1
	Lind et al. (2010)[c]	552 Nuclear Families	2	6p22 (*DCDC2*)	Association	21	2	2	1	2		2			
Calgary (CA)	Field and Kaplan (1998)	79 Nuclear/Extended Families	2	6p22-21	Association	7	X								
					Linkage	7	X								
	Petryshen et al. (2000)	79 Nuclear/Extended Families	2	6p25–21	Linkage	7			X		X	X	X		
	Petryshen et al. (2001)	96 Nuclear/Extended Families	4	6q11–16	Association	68	X								
					Linkage	17	(2.8)		(2.1)	(3.3)	X	1			
	Petryshen et al. (2002)	96 Nuclear/Extended Families	3[a]	2p16	Linkage	7	(2.3)		X		X	(3.8)			
	Hsiung et al. (2004)	100 Nuclear/Extended Families	7[a]	11p15	Association	5	X								
					Linkage	14	(3.6)								
	Tzenova et al. (2004)	100 Nuclear/Extended Families	8[a]	1p36-34	Association	12	X								

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Collection	Publication	Samples	DXY#	Location (*Gene*)	Analysis	Markers	Phenotype[a,b]								
							RD	SWR	PD	oc	PA	SA	RAN	PM	STM/ WM
					Linkage	12	(3.7)		(1.7)		X	(4.0)	X		
Cardiff (UK)	Morris et al. (2000)	77 and 101 Family Trios	1	15q21 (*DYX1C1*)	Association	8	3								
	Turic et al. (2003)[c,d]	77 and 101 Family Trios	2	6p22 (*KIAA0319*)	Association (Haplotype)	22	2	3	2	2	3	2	2	X	
	Morris et al. (2004)	164 Cases and 174 Controls		15q15	Association	47	1								
	Cope et al. (2004)	247 Family Trios	1	15q21 (*DYX1C1*)	Association	3	X	X	X	X	X	X	X	X	
	Cope et al. (2005)	223 Cases and 273 Controls; 143 Family Trios	2	6p22 (*KIAA0319*)	Association	137	3								
	Harold et al. (2006)	350 Cases and 273 Controls	2	6p22 (*KIAA0319*; *DCDC2*)	Association	42	3								
CLDRC (US)	Gayán et al. (1999)	79 Nuclear Families	2[a]	6p22	Linkage	8		X	(2.4)	(3.1)	(1.5)				
	Kaplan et al. (2002)[c]	104 Nuclear Families	2[a]	6p22 (*KIAA0319*; *DCDC2*)	Association	29	2	X	X	2	1				
					Linkage	29	X	R	X	1	R				
	Fisher et al. (2002)	119 Nuclear Families	(2, 3, 5, 6)[a]	Genome Scan	Linkage	401		1	1	1	1				
	Deffenbacher et al. (2004)[b]	349 Nuclear Families	2[a]	6p22 (*DCDC2*)	Association	31	2	3	2	2	2				
					Linkage	22	X	X	X	1	X				
	Francks et al. (2004)	124 Nuclear Families	2[a]	6p22 (*KIAA0319*)	Linkage	21		2	1		1	1			
	Meng et al. (2005b)[c]	153 Nuclear Families	2	6p22 (*KIAA0319*; *DCDC2*)	Association	147	3	1	1	1	2				
	Meng et al. (2005a)[c]	150 Nuclear Families	1	15q21.3 (*DYX1C1*)	Association	2	X	X	X	X	X				
					Linkage	2	X	X	X	X	X				
Dutch	de Kovel et al. (2004)	1 Multiplex Family	9[a]	Genome Scan	Linkage	374	(3.7)	(1.7)	(2.0)				(1.5)	(2.3)	
	de Kovel et al. (2008)	108 Nuclear Families	(1,3,7, 8)[a]	Replication	Linkage	67	(2.3)								

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Collection	Publication	Samples	DXY#	Location (*Gene*)	Analysis	Markers	Phenotype[a,b]								
							RD	SWR	PD	oc	PA	SA	RAN	PM	STM/ WM
Finnish	Nopola-Hemmi et al. (2000)[d]	2 Multiplex Families	1[a]	15q21	Fish	N/A	+								
	Nopola-Hemmi et al. (2001)	1 Multiplex Family	5	Genome Scan	Linkage	320	(3.8)								
	Kaminen et al. (2003)	11 Extended Families	3[a]	Genome Scan	Linkage	376	(2.8)								
	Taipale et al. (2003)	58 Cases and 61 Controls	1	15q21 (*DYX1C1*)	Association	8	2								
	Peyrard-Janvid et al. (2004)	11 Extended Families		2p11; 7q32	Association	45	3								
					Linkage	45	(3.0)								
	Hannula-Jouppi et al. (2005)[d]	1 Multiplex Family	5	3p13-11q (*ROBO1*)	Association	21	+								
	Anthoni et al. (2007)	11 Multiplex Families		2p12	Association	51	2								
German	Schulte-Körne et al. (1998)	7 Extended Families	1[a], 2	6p21-p22; 15q21	Linkage	39	(2.2)								
	Schumacher et al. (2006b)[c]	82 Nuclear Families	6	18p11-q12	Linkage	14	X	X		X	X		X		
	Schumacher et al. (2006a)[c]	137 and 239 Family Trios	2	6p22-21 (*KIAA0319*; *DCDC2*)	Association	29	2	X		X	X		X		
	Anthoni et al. (2007)	251 Nuclear Families		2p12	Haplotype	33	2								
	Schumacher et al. (2008)	82 Nuclear Families	1[a]	15q15–21	Association	19	3	X	X	X	X		X		
					Linkage	19	(1.3)	X	X	X	X		X		
	Ludwig et al. (2008a)	244 Family Trios	2	6p22 (*KIAA0319*; *DCDC2*)	Association	6	X	X	X		X	X			
	Ludwig et al. (2000b)	396 Family Trios	2	6p22 (*DCDC2*)	Association	10	X	1	X		X	X			
	Ludwig et al. (2010)	397 Nuclear Families		12p13	Association	66	1								1
	Dahdouh et al. (2009)	366 Family Trios	1	15q21 (*DYX1C1*)	Association	6	1	X	X	X	X	X	X		1

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Collection	Publication	Samples	DXY#	Location (*Gene*)	Analysis	Markers	Phenotype[a,b]								
							RD	SWR	PD	oc	PA	SA	RAN	PM	STM/ WM
German (2)	Wilcke et al. (2009)	72 Cases and 184 Controls	2	6p22 (*DCDC2*)	Association	3	3								
Indian	Saviour et al. (2008)	52 Cases and 51 Controls	2	6p22 (*DCDC2*); 15q21 (*DYX1C1*)	Association	4	X								
Italian	Marino et al. (2003)[c]	130 Family Trios	7	11p15;11q12; 3q13; 12p12	Association	4	X								
	Marino et al. (2004)	121 Family Trios		15q15	Association	6	1								
	Marino et al. (2005)	158 Nuclear Families	1	15q21 (*DYX1C1*)	Association	3	X	X	X	X					
	Marino et al. (2007)[c]	194 Nuclear Families	1	15q21 (*DYX1C1*)	Association	2	1	2	1	1					2
Italian (2)	Bellini et al. (2005)	57 Cases and 96 Controls	1	15q21 (*DYX1C1*)	Association	3	1								
Norwegian	Fagerheim et al. (1999)	1 Multiplex Family	3	Genome Scan	Linkage	307	(4.3)								
Orton (US)	Grigorenko et al. (1997)	6 Extended Families	(1, 2)[a]	6p23-21; 15, 16	Linkage	17	X	(3.2)	X		2				
	Grigorenko et al. (2000)[c]	8 Extended Families	2[a]	6p22	Linkage	9	R	R	R		R	R	R		
	Grigorenko et al. (2001)[c,d]	8 Extended Families	8	1p36-34	Linkage	12	+	+	+		+		+		
	Grigorenko et al. (2003)	8 Extended Families	2[a]	6p22-21	Linkage	30	(2.0)	R	X		(2.6)		X		
Oxford (UK)	Fisher et al. (1999)	82 Nuclear Families	2[a]	6p21–25	Linkage	15	R	1	1	1	1				
	Fisher et al. (2002)	89 and 84 Nuclear Families	(2, 3, 5, 6, 7)[a]	Genome Scan	Linkage	401		2	2	1	1				
	Marlow et al. (2003)	89 and 84 Nuclear Families	(2, 6)[a]	Genome Scan	Linkage	417		2	2	2	1	1			
	Scerri et al. (2004)	264 Nuclear Families	1	15q21 (*DYX1C1*)	Association	6		X	1	X	X	X			
					Linkage	10		X	X	1	X	X			
	Francks et al. (2004)	264 Nuclear Families	2[a]	6p22 (*KIAA0319*)	Linkage	19		X	(3.3)	(3.5)	X	X			
					Association	57		3	2	3	3	2			

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Collection	Publication	Samples	DXY#	Location (*Gene*)	Analysis	Markers	Phenotype[a,b]								
							RD	SWR	PD	oc	PA	SA	RAN	PM	STM/ WM
	Harold et al. (2006)	264 Families	2	6p22 (*KIAA0319*; *DCDC2*)	Association	57		3	2	3	2	2			
	Dennis et al. (2009)	264 Nuclear Families	2	6p22 (*KIAA0319*; *DCDC2*)	Association	60		3	1	3	1	2			
Seattle (US)	Chapman et al. (2004)	111 Nuclear and Extended Families	1[a], 2, 3, 6	2p; 6p; 15q; 18p	Linkage	32		(2.3)	X						
	Raskind et al. (2005)	108 Nuclear and Extended Families		Genome Scan	Linkage	375			(3.0)						
	Igo et al. (2006)	108 Nuclear and Extended Families		Genome Scan	Linkage	378		(2.9)							
	Brkanac et al. (2007)	191 Family Trios	1–2	6p22 (*KIAA0319*; *DCDC2*); 15q21 (*DYX1C1*)	Association	10	1	1	X			1			
	Brkanac et al. (2008)	144 Nuclear and Extended Families		Genome Scan	Linkage	405								(3.2)	
Tanzanian	Grigorenko et al. (2007b)	88 Family Trios	(1, 2, 3)[a]	2p; 6p; 15q	Linkage	47		(3.8)			X		X	(3.3)	(4.8)
TEDS (UK)	Meaburn et al. (2008) (~100 K SNP Microarray)	5760 Children		Genome Scan	Association	23	2								
Toronto (CA)	Wigg et al. (2004)[c]	148 Nuclear Families	1	15q21 (*DYX1C1*)	Association	6	1	1	1		1	1	1	1	
	Couto et al. (2008)[c]	291 Nuclear Families	8	1p34 (*KIAA0319L*)	Association	5	1	X							
	Couto et al. (2010)	291 Nuclear Families	2	6p22 (*KIAA0319*; *DCDC2*)	Association	37	1	X	1			1			
						Total	66	49	47	32	39	25	15	7	6
						Phenotype	RD	SWR	PD	OC	PA	SA	RAN	PM	STM/ WM

Abbreviations: Reading Disability (RD) phenotype includes categorical definitions and continuous RD phenotypes (Continuous phenotypes described below; *SWR* single-word reading; *PD* Phonological Decoding; *OC* Orthographic Coding; *PA* Phonological Awareness; *SA* Spelling; *RAN* Rapid Naming; *PM* Phonological Memory; *STM* and *WM* Short-term/Working Memory typically tested with Letter/ Digit span tasks

[a] Susceptibility loci confirmed by the linkage study

[b] Significance thresholds for individual phenotypes. Association *P* values are categorized as follows: X = Not Significant; 1: ≤.05; 2: ≤.01; 3: ≤.001

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Linkage: LOD scores are presented in parentheses. *P*-values are categorized as follows: X = not significant; 1: ≤.000741 (suggestive significance, LOD 2.2); 2: ≤.000022 (significant, LOD 3.6); 3: ≤.0000003 (highly significant, LOD 5.4), *R*: ≤.01 (replication of susceptibility region, LOD 1.2) (Lander and Kruglyak 1995)

[c]Phenotypes tested in addition to the nine on the table

Luciano et al. (2007b): bivariate RD phenotype testing irregular word reading within sentences (CCRT) and regular and irregular words lists (SGWRT). A continuous RD phenotype based on a principal component score from the sum of six reading and spelling subtests of regular, irregular, and non-words

Luciano et al. (2007a): cognitive phenotypes from the Multi-dimensional Aptitude Battery (MAB) (including subtets: Information, Vocabulary, Arithmetic, Object Assembly, Spatial; and Verbal IQ, Performance IQ, Full-Scale IQ scores), the digit symbol test from the Wechsler Adult Intelligence Scale (WAIS); speed of processing phenotypes were tested with the choice reaction time and inspection time tests; and two RD phenotypes (CCRT and SGWRT)

Bates et al. (2008): full-scale IQ (MAB), letter-number sequencing subtest, and head circumference

Lind et al. (2010): continuous RD phenotype based on a principal component score from Luciano et al. (2007)

Turic et al. (2003): vocabulary (WISC-III) and attention-deficit-hyperactive-disorder (ADHD) using the Abbreviated Connor's Questionnaire

Kaplan et al. (2002), Deffenbacher et al. (2004), Francks et al. (2002), and Meng et al. (2005a, b): continuous RD phenotype based on a weighted composite of the reading recognition, RC, and spelling subtests (Peabody Individual Achievement Test, PIAT)

Schumacher et al. (2006a): word reading phenotype including both regular and nonword items

Marino et al. (2003): ADHD by interviewing the child, one parent, and teacher

Marino et al. (2007): reading speed and accuracy of meaningful material

Grigorenko et al. (2000, 2001): vocabulary (WISC, Wechsler 1974, 1981); lifelong diagnosis based on participants' history

Grigorenko et al. (2003): two composite phenotypes defined by deficits in (1) PA, PD, and SWR or (2) PA, RAN, and SWR

Wigg et al. (2004): categorical RD phenotype based on SWR, PD, and WRAT-III reading test; continuous RD phenotype based on the WRAT-III reading test; receptive and expressive language (CELF-3)

Couto et al. (2008): tested word reading with a composite of SWR and PD

[d]Studies presented values incongruent with the table's criteria. A plus sign (+) is used to indicate positive results

Grigorenko et al. (2001): displayed consistently positive trends towards significance on chromosome 1p using component phenotypes, but failed to reach the thresholds provided

Turic et al. (2003): found no significant relationship between SWR, PD, OC, PA, SA, RAN, PM and haplotype D6S109/422/1665 on chromosome 6p

Hannula-Jouppi et al. (2005): linked a specific haplotype of *ROBO1* (*DYX5*) to a large pedigree of 21 dyslexic individuals, which displayed reduced expression

Poelmans et al. (2009): reported four new dyslexia candidate genes (Chr. 21q22.3) using FISH and SNP microarray analysis in a sample of one father and three sons

Couto et al. (2010): performed a haplotype analysis and achieved significance using a composite of SWR and PD, and RAN (colors/objects)

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Table 2

Cross-collection inclusion criteria

Collection[a]	Recruit[b]	Inclusion tests[c]	SRD Affected Status[a]	IQ[d]
Brisbane (Australia) (Lind et al. 2010)	Twin Registry	SWR_{IW}, SWR_{RW}, PD, SA_{IW}, SA_{RW}, SA_{NW}	Score 1 SD below group mean on principal component factor score comprised of the six reading and spelling scores	
Calgary (CA) (Hsiung et al. 2004)	Special Schools	PA, PD, SA, RAN	Tests reviewed by two reading disability specialists. Affected status determined primarily from a 2-year gap between chronological age and performance	
Cardiff (UK) (Cope et al. 2005)	Special Schools	SWR	Score 2.5 SD below chronological age norm	85
CLDRC (US) (Deffenbacher et al. 2004)	Twin Registry	DFS of reading Recognition, Reading, Comprehension, and SA	Discriminate score was 1.4 SD below population mean	80
Dutch (De Kovel et al. 2004)	General Public	SWR, PD, IQ	(1) Below 10th percentile on SWR or PD; or (2) below 25th percentile on both measures; or (3) a discrepancy ≥60% between SWR or PD, and IQ	
Finnish (Kaminen et al. 2003)	Clinical Referral	SWR_A, PD_A, SA_{RW}, SWR_F, PD_F, SA_{NW}	Score 2 years below chronological age norm on reading related measures	85
German (Dahdouh et al. 2009)	Clinical Referral	SA	Discrepancy of 1 SD between SA and IQ	85
Italian (Marino et al. 2005)	Clinical Referral	TR_A, TR_F, SWR_A, SWR_F, PD_A, PD_F	(1) 2 SD below population norm on TR_A and TR_F, (2) 1.5 SD below norm on TR_A or TR_F and 2 SD below norm on 1 additional measure	85
Norwegian (Fagerheim et al. 1999)	N/A	SWR_A, SWR_F, PD_A, PD_F, SA_{RW}, SA_{IW}, PA, Education History	Cut off points based on family distribution and population norms	
			Model (1) History or Test Scores	
			Model (2) History and Test Scores	
			Model (3) History or Test Scores, >19 years old	
Orton (US) (Grigorenko et al. 2003)	Family Registry	SWR, PD, PA, RAN	Below the 10th percentile on SWR and another reading subtest	
Oxford (UK) (Fisher et al. 1999)	Clinical Referral	SWR	Discrepancy greater than 2 SD between SWR and IQ	
Seattle (US) (Raskind et al. 2005)	Clinical Referral	SWR_A, SWR_F, PD_A, PD_F, TR_A, TR_F, PM, SA_W, SA_{NW}, Handwriting Automaticity	Discrepancy score of 1 SD below IQ score on 1 of 10 reading measures	90
Toronto (CA) (Couto et al. 2010)	Special Schools	PD_F, SWR_F, SWR_A	1.5 SD below the mean norm on 2 of 3 Tests or Average of 1 SD the mean norm on all three	80

[a] SRD Affected Status describes the selection criteria for each collection. Inclusion criteria have changed slightly in some collections between studies. Therefore, the cited publication specifically follows the named inclusion criteria

[b] Recruit, refers to the type of population from which the sample was ascertained: Special schools, students in special education classes for SRD; Clinical Referral, individuals recruited through learning disorder clinics; or Registries Twin/Family, which were large registries that are typically used for multiple types of medical and psychological studies; General Public, which advertised studies across the general populous

[c] Inclusions tests refer to the reading-related measures that were used to determine inclusion status

[d] IQ cutoffs for inclusion