The Genetic Architecture of SLD

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Specific Learning Disorder (SLD) is a multifactorial, neurodevelopmental disorder which may involve persistent difficulties in reading (dyslexia), written expression and/or mathematics. Dyslexia is characterized by difficulties with speed and accuracy of word reading, deficient decoding abilities, and poor spelling. Several studies from different, but complementary, scientific disciplines have investigated possible causal/risk factors for SLD. Biological, neurological, hereditary, cognitive, linguistic-phonological, developmental and environmental factors have been incriminated. Despite worldwide agreement that SLD is highly heritable, its exact biological basis remains elusive.

specific learning disorder (SLD) dyslexia dyscalculia genetic variants susceptibility

1. Introduction

Specific Learning Disorder (SLD) is a complex disorder with varying manifestations and considerable differences in interpersonal characteristics, albeit present worldwide. According to DSM-5 and the National Joint Committee on Learning Disabilities (NJCLD), SLD is a general term that refers to a group of disorders [1][2][3], which may involve difficulties in reading (dyslexia), written expression (dysgraphia) and/or mathematics (dyscalculia), albeit not accounted for by low intelligence (IQ), sensory acuity (visual problems), poor learning opportunities, or developmental delay (e.g., intellectual disability). Learning disabilities may co-occur with the aforementioned impairments, but are not the result of these conditions [1][4].

The prevalence of SLD varies between 3–12% among the general population, depending on factors such as stringency of measurement cut-offs used for identification [5][6][7], country and level of phonological transparency of the spoken language, sex (male:female ratio 2–3.7:1) [8][9][10], age of assessment, different theoretical perspectives as regards causality, and assessment tools criteria used [6][11]. DSM-5 describes SLD as a neurodevelopmental disorder with a biological origin, which includes an interaction of genetic, epigenetic, and environmental factors. SLD is readily apparent in the early school years in most individuals; symptoms are usually detected when students show a learning profile which is qualitatively lower than their chronological and mental age. However, in some cases, difficulties may become obvious at a later age, when the academic demands rise and exceed the individual's limited capacities, for example during adolescence or adulthood [2][12]. SLD is a lifelong disorder; its impact can have undesirable outcomes for children, as well as for older individuals, on educational, social, financial and occupational level.

Several studies originating from different scientific fields have tried to investigate the possible causal and/or risk factors of SLD. Neurological-neuroanatomical, biological (genetic, epigenetic), cognitive-information processing,

linguistic-phonological, developmental and environmental factors have been incriminated. However, until presently, scientific communities worldwide have not come to an agreement as regards to the exact causes and nature of SLD, neither have they agreed to a commonly accepted definition [13][14][15]. Issues of comorbidity make differential diagnosis an even more complicated task [16]. Arithmetic, reading, or spelling deficits are common in cases with already existing problems in one academic domain compared to the general population [17]; increased dyscalculia rates are observed in families of children with dyslexia [18]. Additionally, dysgraphia rarely occurs alone and frequently co-occurs with dyslexia [19]. Moreover, it is not uncommon for individuals with SLD to show symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), Specific Language Impairment (SLI), motor-coordination deficiencies, emotional-behavioral difficulties, anxiety, depression, personality disorders, or other conditions; it is not clear whether these conditions comorbid with SLD as simultaneous disorders or are secondary problems deriving from the ongoing academic failure. Nevertheless, each year, a considerable number of children and adolescents as well as adults are referred to diagnostic centers seeking help with their learning difficulties [12][20][21].

From the genetics perspective, SLD is a complex disorder with a strong genetic component; heritability estimates from family and twin studies vary between 40–70% (h^2 = 0.52 for dyslexia and 0.61 for dyscalculia) [22][23][24]. Moreover, reading-related abilities such as word recognition, phoneme awareness, orthographic choice, and phoneme decoding have shown significant heritability estimates above 50% [25]. These high heritability estimates were calculated based on twin studies; a proportion of this genetic component can be attributed to common variants of the human genome, such as single nucleotide polymorphisms (SNPs). According to the latest genome-wide association study (GWAS) on dyslexia, SNP-based heritability yielded an estimate of 20% or 25%, assuming a dyslexia prevalence of 5% or 10%, respectively [26]. The remaining of the genetic risk or “missing heritability” of dyslexia could be potentially explained by other types of genomic variants, such as copy number variants (CNVs) and rare variants. The identification of the latter type of variants requires different methodological and analytical approaches, such as massive parallel deep sequencing, also known as next-generation sequencing (NGS).

2. Exploring Genetic Susceptibility to SLD—The Early Times

SLD appears to aggregate in families; the relative risk of SLD in reading or mathematics is substantially higher (4–8 times and 5–10 times higher, respectively) in first-degree relatives of individuals with these learning difficulties [1][27][28]. Family history of reading difficulties and parental literacy skills, as well as mathematical difficulties, predict literacy problems or SLD in offspring, indicating the combined role of genetic and environmental factors [1][29][30]. Back when the first efforts to determine the genetic basis of dyslexia started to appear in the literature (Table 1), the disorder was assumed to follow an autosomal dominant inheritance pattern with high, but incomplete, penetrance [31][32]. In the next two decades, it became clear that SLD, and specifically dyslexia, is a complex disorder with marked genetic heterogeneity, as manifested by the identification of at least nine genetic loci spread throughout the genome (Table 1).

Clues into the genetic underpinnings of reading-related traits originally emerged from classical, hypothesis-free, genome-wide linkage screens, linkage analysis in well-phenotyped pedigrees with multiple affected cases, or the detection of rare chromosomal aberrations (mostly translocations) in dyslexic individuals, likely disrupting a

susceptibility locus. Owing to the prior view of dyslexia as an autosomal dominant disorder, Online Mendelian Inheritance in Man curates these earlier reports [33]. Briefly, more than nine loci have been identified as candidates for susceptibility to SLD, with several genes, particularly *DYX1C1*, *ROBO1*, *KIAA0319*, and *DCDC2*, repeatedly linked to the disorder and/or measures of reading processes disturbed in dyslexia. Overall, many excellent reviews have covered the earlier efforts to unravel the genetic component of dyslexia [34][35][36][37]. Thus, instead of presenting a redundant text herein, we have compiled the seminal studies that led to the identification of dyslexia-associated genes and loci in Table 1. Apart from the categorical diagnosis, we have also recorded quantitative traits often used as proxies (or endophenotypes) to address the general dyslexia phenotype. This is a common approach successfully used to draw closer to the underlying genetic deficit in complex phenotypes [38]. However, the correlation between these endophenotypes and genetic susceptibility markers is far from optimal, since either the same locus has been associated with different SLD-related traits in different studies [39], or the same quantitative trait has shown marked genetic heterogeneity (Table 1).

Following up on gene mapping, a significant number of studies explored associations between specific variants in candidate susceptibility genes and SLD domains or related traits; we summarize the data in Table 2. Then, for the rest of the review, we focus on the latest advances in the field, considering the shift in the analytical approaches used, driven by the advent of high-throughput genotyping technologies and NGS. We discuss the most recent studies in the text and provide a compilation in Table 3.

Less is known about the genetics of mathematical abilities or written expression skills, with few genetic studies conducted thus far (Table 1, Table 2 and Table 3). In nearly half of SLD cases, dyslexia and dyscalculia co-occur [40]. This co-occurrence is more frequent than expected by chance and could be partially attributed to shared genetic influences, according to the “generalist genes” hypothesis [41][42]. However, there are still very limited genetic data to support such shared genetic influences [43][44].

Table 1. Earlier studies (1993–2013) presenting evidence for association of genomic loci with SLD and/or related traits.

Phenotype Domain/Trait	Locus (Gene(s)) [1]	Means of Identification	Reference
	Classical DYX loci		
Dyslexia/SWR	15q15-q21 (**DYX1**)	Locus-specific linkage analysis	[45]
Severe dyslexia/PA	15q21 (*DYX1C1*)	Chromosomal translocation	[46]
Dyslexia/PA	6p22-p21 (**DYX2**)	Locus-specific linkage analysis	[45]

Phenotype Domain/Trait	Locus (Gene(s)) [1]	Means of Identification	Reference
Dyslexia	6p22 (*KIAA0319*, *DCDC2*)	Linkage analysis and association	[47]
Dyslexia	6p22 (*KIAA0319*)	Linkage analysis and association	[48]
Reading disability	6p22 (*KIAA0319*)	Linkage disequilibrium mapping	[49]
Severe dyslexia	6p22-p21 (*DCDC2*)	Linkage disequilibrium mapping	[50]
Dyslexia/RAN	6p21 (separate from DYX2)	Genome-wide linkage scan	[51]
Dyslexia	2p16-p15 (**DYX3**)	Genome-wide linkage scan	[52]
Dyslexia	2p (**DYX3**)	Locus-specific linkage analysis	[25]
Dyslexia/word- and non-word reading, RAN	2p (**DYX3**)	Locus-specific linkage analysis	[39]
Dyslexia	2p12 (*MRPL19*, *C2orf3*)	Linkage disequilibrium mapping	[53]
Spelling	6q11.2-q12 (**DYX4**)	Genome-wide linkage scan	[54]
PA, naming speed, verbal short-term memory	3p12-q13 (**DYX5**)	Genome-wide linkage scan	[55]
	3p12 (*ROBO1*)	Chromosomal translocation	[56]
SWR, PA (reading-related processes)	18p11.2 (**DYX6**)	Genome-wide linkage scan	[57]

Phenotype Domain/Trait	Locus (Gene(s)) [1]	Means of Identification	Reference
Dyslexia		(QTL-based)	
	18p11.2-q12.2	Locus-specific linkage analysis and association	[58]
	(*MC5R*, *DYM*, *NEDD4L)*		
Dyslexia	11p15.5 (**DYX7**)	Linkage analysis and association	[59]
Severe dyslexia/speech development	1p22	Chromosomal translocation	[60]
Dyslexia	1p36-p34 (**DYX8**)	Chromosomal translocation	[61]
Dyslexia/RAN	1p (**DYX8**)	Locus-specific linkage analysis	[62]
Dyslexia/spelling	1p36-p34 (**DYX8**)	Genome-wide linkage scan (QTL-based)	[63]
Dyslexia/word- and non-word reading, RAN	1p36 (**DYX8**)	Locus-specific linkage analysis	[39]
Dyslexia	Xq27.3 (**DYX9**)	Genome-wide linkage scan	[9]
Dyslexia		SNP-based linkage analysis	[64]
	Other loci and genes		

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Disabilities (SLD)1: What Are the Implications? Available online: (accessed on 2 April 2021).

4. National Joint Committee on Learning Disabilities—Definition of Learning Disabilities. Available online: (accessed on 2 April 2021).

Phenotype Domain/Trait	Locus (Gene(s)) [1]	Means of Identification	Reference
Dyslexia/PD, SWR	21q22.3	FISH/SNP 500k NspI microarray (microdeletion—single family)	[65]
	(*PCNT*, *DIP2A*, *S100B*, and *PRMT2*)		
Dyslexia	15q21.2 *(CYP19A1)*	FISH/SNP genotyping and functional studies	[66]
	(separate from *DYX1C1*)		
Dyslexia	4q13, 16p12, 17q22;	Genome-wide linkage scan	[67]
	suggestive locus at 7q36		
Mathematical (dis)abilities	A score of a set of 10 SNPs in 10 loci, accounting for 2.9% of the variance in math ability	GWAS—Discovery (1200 cases) and validation (2356 cases) cohorts (UK population)	[68]

[1] Genomic loci as presented in the original corresponding article. SWR: single-word reading, PD: phonological decoding, RAN: rapid automatized naming, PA: phonological awareness, GWAS: Genome-Wide Association Study.

Table 2. Summary of association studies of established or candidate SLD/dyslexia genes.

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Genes Residing in Classical DYX Loci				

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13. Habib, M. The neurological basis of developmental dyslexia: An overview and working hypothesis. Brain 2000, 123, 2373–2399.
14. Protopapas, A.; Parrila, R. Is Dyslexia a Brain Disorder? Brain Sci. 2018, 8, 61.
15. Ramus, F.; Altarelli, I.; Jednoróg, K.; Zhao, J.; di Covella, L.S. Neuroanatomy of developmental dyslexia: Pitfalls and promise. Neurosci. Biobehav. Rev. 2018, 84, 434–452.
16. Gerber, P.J. The Impact of Learning Disabilities on Adulthood: J. Learn. Disabil. 2011, 45, 31–46.
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Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dyslexia/PA, RAN, and other traits	*DYX1C1*	rs11629841 and haplotypes of rs11629841 with rs3743204 and rs692691	148 nuclear families (470 individuals)	[69]
Dyslexia	*DYX1C1*	No association	264 nuclear families (1153 individuals)	[70]
Dyslexia	*DYX1C1*	c.1249G>T coding variant	191 trios	[71]
Dyslexia/short-term memory	*DYX1C1*	c.−3G>A and c.1249G>T minor alleles haplotype	212 nuclear families (677 individuals)	[72]
Dyslexia/short-term memory	*DYX1C1*	rs3743205/rs3743204/ rs600753 haplotype in females	366 trios	[73]
Reading ability (reading and spelling traits)	*DYX1C1*	rs17819126 coding variant	284 DZ twins, 164 DZ twin families, 143 MZ twin families	[74]
Dyslexia/Reading ability (12 cognitive traits)	*DCDC2*	10/31 SNPs in *DCDC2*	153 nuclear families (536 individuals)	[75]

indicator of risk for reading difficulties. Ann. Dyslexia 2017, 67, 259–280.

32. Smith, S.; Kimberling, W.; Pennington, B.; Lubs, H. Specific reading disability: Identification of an inherited form through linkage analysis. Science 1983, 219, 1345–1347.

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dyslexia	*DCDC2*	No association	396 trios	[76]
Dyslexia (severe versus non-severe)	*DCDC2*	rs793862, rs807701, rs80772 and intron-2 deletion	72 cases/184 controls	[77]
Reading ability (7 reading and spelling traits)	*DCDC2*	21 SNPs of which rs1419228 was associated with poorer general reading performance	522 twin families (1067 individuals) (unselected population)	[78]
Dyslexia/word-reading and spelling	*DCDC2*	rs793862 and rs807724 minor alleles in SLD or comorbid cases	225 cases/442 controls (plus 54 comorbid SLD/SLI/ADHD cases)	[79]
Dyslexia and mathematics (numerical facts and mental calculation)	*DCDC2* and *DYX1C1*	c.−3G>A, c.1249G>T in *DYX1C1* and intron-2 deletion/STR in *DCDC2*	180 nuclear families (581 individuals)	[80]
Dyslexia/6 traits of reading ability	*DCDC2*	Intron-2 STR alleles associated with word- and non-word repetition	303 nuclear families (973 individuals)	[81]

45. Grigorenko, E.L.; Wood, F.B.; Meyer, M.S.; Hart, L.A.; Speed, W.C.; Shuster, A.; Pauls, D.L. Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. Am. J. Hum. Genet. 1997, 60, 27–39.

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dyslexia	*DCDC2*	14 SNPs of which several SNPs and two haplotypes were associated under different models	196 cases/196 controls	[82]
Dyslexia/6 traits of reading ability	*DCDC2* and *KIAA0319*	5 SNPs within *KIAA0319* Pairwise associations between a *DCDC2* and a *KIAA0319* variant	264 nuclear families 350 cases/273 controls	[83]
Reading abilities (5 reading and spelling traits)	*KIAA0319*	rs2143340 associated with poor reading and spelling	~6000 individuals	[84]
Dyslexia/6 traits of reading ability	*KIAA0319*	rs9461045 associated with dyslexia traits	264 nuclear families (of which 126 comprised a severity sample)	[85]
Dyslexia/Reading, spelling, and phonological traits	*DCDC2* and *KIAA0319* *NRSN1*	rs6935076 in *KIAA0319* associated with dyslexia and spelling and 3 SNPs in *NRSN1*	291 nuclear families (of which 165 are trios)	[86]
General reading abilities (word-reading	*KIAA0319* and *CMIP*	rs2143340 in *KIAA0319* and rs6564903 in *CMIP*	225 cases/442 controls	[79]

56. Hannula-Jouppi, K.; Kaminen-Ahola, N.; Taipale, M.; Eklund, R.; Nopola-Hemmi, J.; Kääriäinen, H.; Kere, J. The Axon Guidance Receptor Gene ROBO1 Is a Candidate Gene for Developmental

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
and spelling)			(plus 54 comorbid SLD/SLI/ADHD cases)	
Dyslexia and mathematics	*ROBO1*	rs333491 associated with mental calculation accuracy	179 nuclear families (of which 154 comprised a severity sample)	[87]
Dyslexia Word-reading efficiency and RAN	*KIAA0319L* *KIAA0319L*	rs7523017 associated with dyslexia A four SNP-haplotype	291 nuclear families 156 nuclear families	[88]
Other dyslexia-candidate genes				
Dyslexia/6 traits of reading ability	*CNTNAP2*	rs2710102 associated with non-word repetition	188 trios	[89]
Dyslexia/6 traits of reading ability	*FOXP2*	rs7782412 major allele associated with non-word repetition and real-word reading efficiency	188 trios	[89]
Dyslexia (mismatch response)	*SLC2A3*	rs4234898 on chromosome 4 associated	200 cases (discovery set)	[90]

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Genet. 2012, 42, 509–527.

67. Field, L.L.; Shumansky, K.; Ryan, J.; Truong, D.; Swiergala, E.; Kaplan, B.J. Dense-map genome scan for dyslexia supports loci at 4q13, 16p12, 17q22; suggests novel locus at 7q. Genes Brain

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
		with mismatch response	186 cases (replication set)	
Dyslexia/IQ and cognitive processes and mathematics	*GRIN2B*	rs5796555 and rs1012586 associated with dyslexia	466 nuclear families, of which 227 comprised a severity sample	[91]
Reading ability (reading comprehension, phonological memory)	*BDNF*	rs6265 associated with poorer reading performance rs6265 associated with increased brain activity in areas contributing to phonological and reading competence	81 children 94 children	[92] [93]
Dyslexia-associated gene panels				
Dyslexia/word-reading and spelling	*DYX1C1*, *DCDC2, KIAA0319,* and *MRPL19/C2orf3* locus	No association	958 cases/1150 controls	[94]
Dyslexia	*MRPL19, C20RF3, ROBO1, DCDC2, KIAA0319, DYX1C1, CNTNAP2, ATP2C2* and *CMIP*	rs807724 in *DCDC2* associated with dyslexia	331 cases/maximum 363 controls	[95]

in German dyslexics. Ann. Dyslexia 2009, 59, 1–11.

78. Lind, P.A.; Luciano, M.; Wright, M.J.; Montgomery, G.W.; Martin, N.; Bates, T.C. Dyslexia and DCDC2: Normal variation in reading and spelling is associated with DCDC2 polymorphisms in an Australian population sample. Eur. J. Hum. Genet. 2010, 18, 668–673.

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dyslexia/spelling	*CYP19A1, DCDC2, DIP2A, DYX1C1, GCFC2 (C2orf3), KIAA0319, MRPL19, PCNT, PRMT2, ROBO1* and *S100B*	A non-synonymous SNP in *DCDC2* (rs2274305) and a non-coding SNP in *S100B* (rs9722) associated with dyslexia	361 cases/261 controls 575 affected, 376 unaffected and 511 of unknown status (family-based)	[96]
Dyslexia	*DYX1C1, DCDC2, KIAA0319, ROBO1* and *TDP2*	Nominal associations only (rs7765678 in *DCDC2*, rs2038137 and rs6935076 in *KIAA0319*)	383 cases/357 controls	[38]
Reading abilities (Word/Non-word reading fluency, PA, RAN)	*Top hits from previous GWAS on reading (SLD) and language (SLI) (dis)abilities*	No association	307 nuclear families (483 children/505 adults)	[97]
Reading ability	*CYP19A1, DCDC2, DYX1C1, GCFC2 (C2orf3), KIAA0319, MRPL19, ROBO1, KIAA0319L DIP2A, PRMT2, PCNT, S100B, CNTNAP2* and *CMIP*	No single-marker association 62 SNPs—Gene-based SNP-set associations were significant for *DYX1C1, DIP2A, CYP19A1*	1217 old adults (>70 yrs) (unimpaired)	[98]

1p34 as a Candidate for Reading Disabilities. J. Neurogenetics 2008, 22, 295–313.

89. Peter, B.; Raskind, W.H.; Matsushita, M.; Lisowski, M.; Vu, T.; Berninger, V.W.; Wijsman, E.M.; Brkanac, Z. Replication of CNTNAP2 association with nonword repetition and support for FOXP2

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dyslexia Word reading, RAN, and syllable discrimination	*KIAA0319, DCDC2,* and *DYX1C1*	No single-marker association Pairwise SNP association with dyslexia (rs2274305 in *DCDC2* and rs4504469 in *KIAA0319*) rs2274305 in *DCDC2* rs57809907 in *DYX1C1* rs4504469 in *KIAA0319*	286 cases/1197 controls 3357 individuals (total cohort)	[99]
Reading and spelling ability	*CMIP, CNTNAP2, CYP19A1,* *DCDC2, DIP2A, DYX1C1, C2orf3, KIAA0319, KIAA0319L, MRPL19, ROBO1, PCNT, PRMT2* and *S100B*	No association (>9500 SNPs and gene-based SNP-sets)	1505 individuals (unimpaired)	[100]
Other SLD domains				
Reading and mathematical traits indicative of dyslexia and dyscalculia, respectively	15q11.2(BP1-BP2)—*TUBGCP5, NIPA1, NIPA2, CYFIP1*	15q11.2(BP1-BP2) deletion CNV associated with worse outcome in reading and mathematical abilities	167 controls, carriers of neuropsychiatric CNVs	[43]

dyslexia and ADHD candidate genes in a Spanish cohort: Implications of comorbid samples. PLoS ONE 2018, 13, e0206431.

100. Doust, C.; Gordon, S.D.; Garden, N.; Fisher, S.E.; Martin, N.G.; Bates, T.C.; Luciano, M. The Association of Dyslexia and Developmental Speech and Language Disorder Candidate Genes

Phenotype (Trait/Subphenotype)	Gene(s)	Variant(s) Associated with Phenotype or Trait	Sample Size and Study Design	Reference
Dysgraphia	*DCDC2, DYX1C1, KIAA0319* and *ROBO1*	rs3743204 in *DYX1C1* and rs793842 in *DCDC2* associated with dysgraphia measurements	21 cases/18 controls	[101]

PA: phonological awareness, RAN: rapid automatized naming, SNP: single nucleotide polymorphism, cases = dyslexic cases, controls = unimpaired individuals, DZ: dizygotic (twins), MZ: monozygotic (twins), STR: short tandem repeat.

Table 3. Recent studies (2013–2021) reporting novel genomic loci and genes associated with SLD and related traits using high-throughput methodologies.

Phenotype (Trait/Subphenotype)	Gene(s)	Experimental Approach	Reference
Reading abilities (reading, spelling)	Suggestive associations only	GWAS (meta-analysis)	[102]
Dyslexia or Dyslexia+SLI comorbidity	*ZNF385D* (comorbid cases only)	GWAS (case-control)	[103]
Dyslexia (phonological coding skill)	Suggestive linkage and suggestive associations only	GWAS (case-control)	[67]
Dyslexia	*PCDH11X*	CNV + SNP microarray (11 families)	[104]

components of reading disability and language impairment. Genes Brain Behav. 2013, 12, 792–801.

104. Veerappa, A.M.; Saldanha, M.; Padakannaya, P.; Ramachandra, N.B. Genome-wide copy number scan identifies disruption of PCDH11X in developmental dyslexia. Am. J. Med. Genet. Part. B Neuropsychiatr. Genet. 2013, 162, 889–897.

105. Gialluisi, A.; Newbury, D.F.; Wilcutt, E.G.; Olson, R.K.; DeFries, J.C.; Brandler, W.M.; Pennington, B.F.; Smith, S.D.; Scerri, T.S.; Simpson, N.H.; et al. Genome-wide screening for DNA variants

Czamara, D.; Pourcain, B.S.; Brandler, W.; et al. Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia. Transl. Psychiatry 2019, 9, 1–15.

Phenotype (Trait/Subphenotype)	Gene(s)	Experimental Approach	Reference
Dyslexia/Dyscalculia	15q11.2(BP1-BP2) harboring *TUBGCP5, NIPA1, NIPA2* and *CYFIP1*	Targeted CNV and neuroimaging analysis	[43][44]
Reading abilities (reading, spelling, phonological awareness)	*RBFOX2, CCDC136/FLNC*	GWAS (meta-analysis)	[105]
Dyslexia	*NSF*	CNV + SNP microarray (10 families)	[106]
Dyslexia	*CEP63*	WES (single family)	[107]
Dyslexia	*S100B*	Targeted NGS (11 genes panel)	[96]
Dyslexia	*CCDC136* and *FLNC*	Targeted NGS—11 loci harboring 25 genes	[108]
Dyslexia	*NCAN*	SNP microarray and linkage analysis, WES (single family)	[109]
Dyslexia	*PCDHG* gene cluster	SNP microarray and WES (single family)	[110]

KIAA0319 and DCDC2 in Dyslexia. Behav. Genet. 2010, 41, 110–119.

Phenotype (Trait/Subphenotype)	Gene(s)	Experimental Approach	Reference
Dyslexia/8 cognitive traits	*MIR924HG* (associated with RAN)	GWAS (case-control)	[111]
Dyslexia	*VEPH1* (gene-based analysis)	GWAS (case-control)	[26]
Dyslexia	*SPRY1*	SNP microarray and linkage analysis (single family)	[112]
Reading ability (word reading)	*LINC00935* and *CCNT1*	GWAS (case-control)	[113]
Mathematical abilities	*MYO18B*	GWAS (case-control)	[114]
Mathematical abilities	rs789859 intergenic to *LSG1* and *FAM43A* (3q29)	GWAS (high versus low mathematical ability)	[115]
Mathematical abilities	*SPOCK1*	GWAS (meta-analysis)	[116]

SLI: specific language impairment, GWAS: Genome-Wide Association Study, WES: whole exome sequencing, CNV: copy number variant, SNP: single nucleotide polymorphism.

3. High-Throughput Genome-Wide Analysis Continues to Shed Light on the Genetic Architecture of SLD

3.1. Genome-Wide Association Studies (GWAS) and Polygenic Risk Scores (PRSs)

134. Carvalho, M.R.S.; Vianna-Jorge, R.; Oliveira, L.D.F.S.; Costa, A.L.F.; Pinheiro-Chagas, P.; Stutzenstein, P.; Zeni, P.R.G.; Rosa, R.F.M.; De Aguiar, M.J.B.; Haase, V.G.; Are 22q11.2 distal deletions associated with math difficulties? Am. J. Med. Genet. Part. A 2014, 164, 2256–2262.

135. Mitrakos, A.; Sofokleous, C.; Papadimas, G.; Fryssira, H.; Kitsiou-Tzeli, S.; Tzetis, M.; Kosma, K. A Female Patient with Xq28 Microduplication Presenting with Myotubular Myopathy, Confirmed with a Custom-Designed X-array. Neuropediatrics 2018, 50, 061–063.

136. Davis, J.M.; Searles, V.B.; Anderson, N.; Keeney, J.; Raznahan, A.; Horwood, L.J.; Fergusson, D.M.; Kennedy, M.A.; Giedd, J.; Sikela, J.M. DUF1220 copy number is linearly associated with increased cognitive function as measured by total IQ and mathematical aptitude scores. Qual. Life Res. 2014, 134, 67–75.

137. Popesco, M.C.; MacLaren, E.J.; Hopkins, J.; Dumas, L.; Cox, M.; Meltesen, L.; McGavran, L.; Wyckoff, G.J.; Sikela, J.M. Human Lineage-Specific Amplification, Selection, and Neuronal Expression of DUF1220 Domains. Science 2006, 313, 1304–1307.

138. Dehaene, S.; Piazza, M.; Pinel, P.; Cohen, L. Three Parietal Circuits for Number Processing. Cogn. Neuropsychol. 2003, 20, 487–506.

139. Ischebeck, A.; Zamarian, L.; Schocke, M.; Delazer, M. Flexible transfer of knowledge in mental arithmetic—An fMRI study. Neuroimage 2009, 44, 1103–1112.

140. Butterworth, B.; Varma, S.; Laurillard, D. Dyscalculia: From Brain to Education. Science 2011, 332, 1049–1053.

141. Luo, R.; Sanders, S.J.; Tian, Y.; Voineagu, I.; Huang, N.; Chu, S.H.; Klei, L.; Cai, C.; Ou, J.; Lowe, J.K.; et al. Genome-wide Transcriptome Profiling Reveals the Functional Impact of Rare De Novo and Recurrent CNVs in Autism Spectrum Disorders. Am. J. Hum. Genet. 2012, 91, 38–55.

142. Huguet, G.; Schramm, C.; Douard, E.; Tamer, P.; Main, A.; Monin, P.; England, J.; Jizi, K.; Renne, T.; Poirier, M.; et al. Genome-wide analysis of gene dosage in 24,092 individuals estimates that 10,000 genes modulate cognitive ability. Mol. Psychiatry 2021, 1–14.

143. Yoon, K.-J.; Nguyen, H.N.; Ursini, G.; Zhang, F.; Kim, N.-S.; Wen, Z.; Makri, G.; Nauen, D.; Shin, J.H.; Park, Y.; et al. Modeling a Genetic Risk for Schizophrenia in iPSCs and Mice Reveals Neural Stem Cell Deficits Associated with Adherens Junctions and Polarity. Cell Stem Cell 2014, 15, 79–91.

144. De Ligt, J.; Willemsen, M.H.; Van Bon, B.W.; Kleefstra, T.; Yntema, H.G.; Kroes, T.; Silfhout, A.T.V.-V.; Koolen, D.A.; De Vries, P.; Gilissen, C.; et al. Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability. N. Engl. J. Med. 2012, 367, 1921–1929.

145. Iossifov, I.; O'Roak, B.J.; Sanders, S.J.; Ronemus, M.; Krumm, N.; Levy, D.; Stessman, H.A.; Witherspoon, K.T.; Vives, L.; Patterson, K.E.; et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature 2014, 515, 216–221.

children [90]. This mismatch, respectively, was also shown to associate with common variants in *DYX1C1* [120], uncommon variants in *DCDC2* and *KIAA0319* [121].

The largest GWAS for dyslexia-specific traits was recently published, with data generated for almost 3500 reading-impaired and typically developing children of European ancestry from nine countries speaking six different languages. Genome-wide significance was observed with RAN for four variants on 18q12.2, within *MIR924HG* (rs17663182), and a suggestive association on 8q12.3 within *NKAIN3*. It is of note that *MIR924* is predicted to regulate candidate dyslexia susceptibility genes like *MRPL19* and *KIAA0319L*, as observed via in silico analysis of putative miR-924 binding sites [111]. The same group performed polygenic risk score (PRS) analysis between eight reading traits and different neuropsychiatric disorders (ADHD, ASD, major depressive disorder and schizophrenia), educational attainment, and neuroimaging phenotypes (seven brain areas) and found a significant genetic overlap between some of these reading traits and educational attainment and, to a lesser extent, with ADHD [111]. This initiative led to an even larger dyslexia case-control GWAS of almost 2300 cases and 6300 controls, a subset of which overlapped with the same authors' 2019 paper [26]. No novel genome-wide significant associations emerged at single-marker level; gene-based analysis from the top SNP association signals revealed *VEPH1* (3q25) as a top candidate gene, but no specific pathways showed significant enrichment [26].

Actually, the first study assessing the reading ability of nondyslexic children and adolescents with the use of PRS analysis was published in 2017. The authors in this study utilized GWAS data from >5800 cases and used educational attainment (=years of education completed) to predict reading performance in English. They calculated a PRS-heritability estimate of reading ability of almost 5%, based only on common variants. This estimate represents approximately 7% of the total heritability for reading ability (h^2 = 70%; 5%/70%) evaluated through twin studies [122]. However, if calculating the PRS-heritability estimate using an SNP-heritability estimate, which was shown to account for 22% of the total genetic variance [123], then the PRS-heritability estimate can explain a significant 23% (5%/22%) of the genetic variance observed for reading ability, an estimate that remained significant after accounting for age-specific cognitive ability and family socioeconomic status [122].

The use of PRSs is a rather young addition to the armor of (statistical) tools to evaluate the genetic component of complex traits, even more so for complex cognitive skills like reading performance; yet, we can already foresee its potential. Given its inherent nature (as DNA variants do not change by age), knowing the individual genetic differences in reading ability perhaps may prove useful in the early prediction of reading problems like dyslexia. This will require large multicentered initiatives of tens of thousands of participants. However, because language transparency is an important issue in assessing dyslexia, perhaps large GWAS with participants using the same language would be powerful enough to explore the applicability of PRS further, an approach already tested by Gialluisi et al. in their 2019 analysis [111].

The first GWAS study conducted to exclusively assess mathematical ability and disability was published ten years ago, two groups of children from the Twins Early Development Study, with high versus low mathematical ability (600 individuals per group), served as the discovery cohort, and 2356 individuals, spanning the entire distribution of mathematical ability, were used for validation purposes. Out of 10 top candidate SNPs, rs11225308 (*MMP7*),

146. Hiraide, T.; Yamoto, K.; Masunaga, Y.; Asahina, M.; Endoh, Y.; Ohkubo, Y.; Matsubayashi, T.; Tsurui, S.; Yamada, H.; Yanagi, K.; et al. Genetic and phenotypic analysis of 101 patients with developmental delay or intellectual disability using whole-exome sequencing. Clin. Genet. 2021.

147. Massinen, S.; Hokkanen, M.-E.; Matsson, H.; Tammimies, K.; Tapia-Páez, I.; Dahlström-Heuser, V.; Kuja-Panula, J.; Burghoorn, J.; Jeppsson, K.E.; Swoboda, P.; et al. Increased Expression of the Dyslexia Candidate Gene DCDC2 Affects Length and Signaling of Primary Cilia in Neurons. PLoS ONE 2011, 6, e20580.

148. Tarkar, A.; Loges, N.T.; Slagle, C.E.; Francis, R.; Dougherty, G.W.; Tamayo, J.V.; Shook, B.; Cantino, M.; Schwartz, D.; Jahnke, C.; et al. DYX1C1 is required for axonemal dynein assembly and ciliary motility. Nat. Genet. 2013, 45, 995–1003.

149. Chandrasekar, G.; Vesterlund, L.; Hultenby, K.; Tapia-Páez, I.; Kere, J. The Zebrafish Orthologue of the Dyslexia Candidate Gene DYX1C1 Is Essential for Cilia Growth and Function. PLoS ONE 2013, 8, e63123.

150. Schueler, M.; Braun, D.A.; Chandrasekar, G.; Gee, H.Y.; Klasson, T.D.; Halbritter, J.; Bieder, A.; Porath, J.D.; Airik, R.; Zhou, W.; et al. DCDC2 Mutations Cause a Renal-Hepatic Ciliopathy by Disrupting Wnt Signaling. Am. J. Hum. Genet. 2015, 96, 81–92.

151. Grati, M.; Chakchouk, I.; Ma, Q.; Bensaid, M.; DeSmidt, A.; Turki, N.; Yan, D.; Baanannou, A.; Mittal, R.; Driss, N.; et al. A missense mutation in DCDC2 causes human recessive deafness DFNB66, likely by interfering with sensory hair cell and supporting cell cilia length regulation. Hum. Mol. Genet. 2015, 24, 2482–2491.

152. Girard, M.; Bizet, A.A.; Lachaux, A.; Gonzales, E.; Filhol, E.; Collardeau-Frachon, S.; Jeanpierre, C.; Henry, C.; Fabre, M.; Viremouneix, L.; et al. DCDC2Mutations Cause Neonatal Sclerosing Cholangitis. Hum. Mutat. 2016, 37, 1025–1029.

153. Grammatikopoulos, T.; Sambrotta, M.; Strautnieks, S.; Foskett, P.; Knisely, A.; Wagner, B.; Deheragoda, M.; Starling, C.; Mieli-Vergani, G.; Smith, J.; et al. Mutations in DCDC2 (doublecortin domain containing protein 2) in neonatal sclerosing cholangitis. J. Hepatol. 2016, 65, 1179–1187.

154. Bieder, A.; Einarsdottir, E.; Matsson, H.; Nilsson, H.E.; Eisfeldt, J.; Dragomir, A.; Paucar, M.; Granberg, T.; Li, T.-Q.; Lindstrand, A.; et al. Rare variants in dynein heavy chain genes in two individuals with situs inversus and developmental dyslexia: A case report. BMC Med. Genet. 2020, 21, 1–9.

155. Trulioff, A.; Ermakov, A.; Malashichev, Y. Primary Cilia as a Possible Link between Left-Right Asymmetry and Neurodevelopmental Diseases. Genes 2017, 8, 48.

156. Mascheretti, S.; Bureau, A.; Battaglia, M.; Simone, D.; Quadrelli, E.; Croteau, J.; Cellino, M.R.; Giorda, R.; Beri, S.; Maziade, M.; et al. An assessment of gene-by-environment interactions in developmental dyslexia-related phenotypes. Genes Brain Behav. 2012, 12, 47–55.

rs3624449 (*GRIK1*), rs1728824 (*DNAH5*) were the variants most significantly associated with mathematical ability. Because the effect sizes of these 10 SNPs were small, the authors created an ‘SNP-set score’ for each of the 2356 individuals, which accounted for 2.9% of the variance in their sample [68]. In fact, by using this SNP-set score, it was shown that one third of children who harbored ≥50% of the identified risk alleles were nearly twice as likely to be in the lowest-performing 15% of the mathematical ability distribution [68]. This score was later correlated with certain environmental factors, demonstrating likely gene × environment interactions [124].

Subsequently, in a sample of almost 700 dyslexic cases and more than 1400 controls, available GWAS data were reanalyzed to associate genetic variation specifically with dyscalculia. The authors found rs133885 in *MYO18B* to be strongly correlated with mathematical abilities in the dyslexia sample and, to a lesser extent, the general population. A significantly lower depth of the right intraparietal sulcus, an anatomical brain region involved in numerical processing in humans, was associated with rs133885 [114]. However, this association was not supported in the subsequent analysis of a much larger collection of 5144 individuals from four cohorts of European ancestry, 329 of which were diagnosed with dyslexia [125]. A third GWAS aiming to explore the genetic contributions to mathematical ability was conducted in a general population sample of 602 adolescents/young adults with excellent verbal ability but either high or low mathematical ability. The marker with the largest effect size was rs789859, located in the promoter of *FAM43A* and in high linkage disequilibrium with two SNPs in the adjacent *LSG1* gene (3q29), a region previously linked to learning difficulties and autism [115]. Although the encoded protein’s function remains obscure, *FAM43A* was found expressed in the brain, cerebellum and spinal cord [115].

One GWAS was conducted exclusively on the purpose to assess mathematical ability in the general population of Chinese elementary school students in 2017. Two discovery and one replication groups were used, totaling almost 1600 individuals. Sample meta-analysis revealed four linked SNPs in *SPOCK1* associated on a genome-wide significance level with a decrease in math scores on two examination periods [116]. Interestingly, mutations in *SPOCK1*, which encodes for the extracellular proteoglycan testican-1, have been associated with ID and microcephaly in humans, whereas *Spock1* mouse models have demonstrated strong gene expression in the brain as well as its role in neurogenesis [116].

By now, it has become clear that because GWAS are designed to target common variants, often in non-coding, regulatory or even intergenic regions, they do not necessarily directly reveal the true effect of likely pathogenic variants, as it would be expected in the case of rare coding variants. On the other hand, initial genome-wide genotyping platforms were designed based on Caucasian genome frequencies and most of what we currently know about reading and mathematical abilities and disabilities originates from studies of individuals of Caucasian ancestry, despite the fact that SLD affects populations globally and irrespective of language. Thus, we are largely unaware of the genetic architecture of SLD *across* populations and ethnic ancestries. GWAS, despite setting the grounds for unbiased genome-wide interrogations, most often than not, have returned results that could be hardly replicated. This has been attributed either to small effect sizes of common variants, especially for quantitative traits such as reading-associated traits, small sample sizes to reveal statistically powerful associations or even to lack of consensus in SLD diagnosis. Hence, alternative yet complementary methods, as those described in the next

paragraphs, have significantly contributed in the delineation of the genetic architecture of SLD during the last years.

3.2. Copy-Number Variants (CNVs)

Part of the missing heritability of SLD may be also caused by structural variants. CNVs have been extensively explored in other neurodevelopmental disorders, such as ASD, ID [126][127][128], Tourette Syndrome [129][130], and SLI [131]; results for SLD have been inconclusive. On one hand, recent analyses of dyslexia cohorts indicate that rare, large CNVs may not confer a significant burden [126][132]. On the other hand, rare de novo or inherited deletions or duplications, such as the Xq21.3 region bearing *PCDH11X* [104], 17q21.31 harboring *NSF* [106], and 15q11.2(BP1-BP2) harboring four highly conserved genes (Table 3) [43][44], have been reported in cases with SLD. Earlier, a father and his three affected sons were found to carry a submicroscopic deletion (at least ~176 kb) on 21q22.3, encompassing the 3′ region of *PCNT*, genes *DIP2A* and *S100B* and the 5′ upstream sequence of *PRMT2*. The deletion perfectly segregated with dyslexia and standard scores for phonological decoding and single-word reading of below −1.5 to −2 standard deviations [65]. As described later (Section 3.3), a non-coding variant in *S100B* was also associated with spelling performance in a German family set [96].

Different loci have been found to harbor deletions and duplications in patients with various clinical presentations and comorbid math comprehension difficulties. Children with the 22q11.2 deletion syndrome show considerable difficulties in procedural calculation and word problem solving due to difficulties in understanding and representing numerical quantities, despite relatively normal reading performance [133]. A 22q11.2 deletion spanning LCR22-4 to LCR22-5 interval was found in an 11-year-old girl with normal intelligence, number sense deficit, normal results in spelling and reading tests and social contact difficulties [134]. A severely affected girl with X-linked myotubular myopathy and math difficulties was found to carry an inherited 661kb Xq28 microduplication with a skewed X chromosome inactivation pattern [135]. If we exclude syndromic cases, reports on individuals presenting exclusively with mathematical impairments who bear rare or novel de novo or inherited CNVs are truly scarce. An increase of CNVs of the Olduvai protein domain on 1q21 (*NBPF15*), previously known as DUF1220, appear to be involved in human brain size and evolution and may determine the mathematical aptitude ability of both sexes [136]. This genetic locus is highly expressed in brain regions with high cognitive function [137], but it has not been studied in the context of mathematical disabilities.

Last but not least, a recent study from the Icelandic population investigated the effect of 15q11.2(BP1-BP2) deletion in cognitive, structural and functional correlations of dyslexia and mathematical disabilities. This CNV was previously associated with cognition deficits in non-neuropsychiatric cases with a history of SLD [43]. Later, Ulfarsson et al. showed that the deletion conferred high risk in either dyslexia or dyscalculia, but the risk was even higher in the combined dyslexia plus dyscalculia phenotype; all deletion carriers performed worse on a battery of tests assessing reading and mathematical abilities. In the same sample, structural magnetic resonance imaging (sMRI) and functional MRI (fMRI) were performed, demonstrating that smaller left fusiform gyrus and altered activation in the left fusiform and left angular gyrus also associated with the 15q11.2 deletion [44]. These brain areas are involved in the retrieval of mathematical facts, the usage of learned facts and the performance of

arithmetic operations [138][139][140]. This anatomical and functional brain differentiation could be one cause of the greater risk observed for the combined phenotype in deletion carriers.

Either de novo or transmitted, these structural variations may produce a yet unknown spectrum of disturbances on genomic, transcriptomic and proteomic level, for instance haploinsufficiency in the case of deletion or overexpression in the case of duplication [141][142], consequently also affecting subsequent protein-protein interactions; these are hypotheses that warrant further investigation. Interestingly, the 15q11.2(BP1-BP2) duplication carriers do not show significant cognitive impairments, compared to 15q11.2(BP1-BP2) deletion carriers, and are comparable to no-CNV controls [44]. This fact supports the role of haploinsufficiency for the genes mapped on this region, particularly *CYFIP1*, which was shown to be involved in neuronal development [143].

3.3. Next-Generation Sequencing

It is unclear how much of the missing heritability of SLD could be attributed to rare or de novo variants of moderate or high effect, even though this issue has been extensively studied with respect to ID, ASD and developmental delay [144][145][146]. With the emergence of NGS technology, the identification of rare variants could help fill in some of the missing pieces of the puzzle. Sequencing data have only recently begun to emerge for SLD, supporting the influence of certain genomic regions on reading performance and related disabilities. As expected, the first efforts concentrated and sources were allocated on the validation of previously established or suspected dyslexia genes in various populations.

Originally mapped through a submicroscopic deletion on 21q22.3 in a dyslexia family [65], *S100B* was one of 11 genes to be scrutinized for rare variants using targeted NGS in more than 900 dyslexia cases from Finland and Germany; a 3′ UTR variant (rs9722), located on or adjacent to in silico predicted miRNA target sites, was associated with spelling performance in the German family set. Moreover, a nonsynonymous variant in *DCDC2* (rs2274305) was associated with severe spelling deficiency in the same sample set [96]. A similar approach was applied to a subsequent next-generation targeted sequencing effort by Adams et al., who selected dyslexia-associated candidate genes to be screened in 96 affected, unrelated subjects of European ancestry from the Colorado Learning Disability Research Center (CLDRC). These cases were selected based on a CLDRC-derived discriminant score indicating impairment in reading ability [108]. The authors searched for rare, likely disrupting, variants and calculated a statistically significant increase in the frequency of observed mutations in dyslexia cases —compared to data from 1000 Genomes Project—in two loci: 7q32.1 harboring the adjacent genes *CCDC136* and *FLNC* (19 missense variants) and 6p22 harboring *DCDC2* and *KIAA0319* (74 missense variants). The data indicate that these regions must have an influence on reading performance, even though not all of the above-mentioned genes show detectable expression in the brain (Figure 1) [108].

The first whole-exome sequencing (WES) study was published in 2015 by Einarsdottir et al. in an effort to identify the genetic basis of a familial form of dyslexia with likely complete penetrance in an extended three-generation pedigree with 12 confirmed dyslexic and four uncertain cases. Through several filtering steps on WES data, a small heterozygous in/del variant was identified in *CEP63*, namely c.686–687delGCinsTT; its transmission was compatible with autosomal dominant inheritance. This rare variant codes for a non-synonymous change in a highly

evolutionarily conserved amino acid (p.R229L), which was in silico predicted to alter the protein's tertiary structure [107]. As discussed later (Section 6), CEP63 is a centrosomal protein involved in microtubule organization and, even though it is ubiquitously expressed (Figure 1), brain-specific isoforms may be affected by such rare variants. It still remains to be seen whether *CEP63* variants are linked to dyslexia in additional cases.

Several other reports have also demonstrated that dyslexia-associated genes encode proteins with structural and functional roles in cilia [147][148][149][150][151][152][153]. Recently, rare variants were identified in two genes related to motile cilia structure and function, namely dynein axonemal heavy chain 5 (*DNAH5*) and dynein axonemal heavy chain 11 (*DNAH11*). This represents the first whole-genome sequencing (WGS) analysis in literature of two unrelated dyslexia cases, with situs inversus and ADHD symptomatology [154]. Even though direct links between visceral and functional brain asymmetry are lacking, visceral asymmetry (e.g., situs inversus) is comorbid, at least in some cases, with psychiatric and neurodevelopmental disorders [155]. Although it could not be proven unequivocally that the identified variants in *DNAH5* and *DNAH11* cause susceptibility to dyslexia, these two genes represent good candidates for further studies.

Overall, the most recent studies that have used state-of-the-art methodology to look for either likely pathogenic CNVs or rare variants in isolated families have provided clues for the implication of novel genes. Family-based studies continue to be a powerful method to unravel the genetic basis of dyslexia [107]. However, variations in reported loci do not explain, so far, but a small percentage of the genetic component of SLD. Consequently, much of the heritability of learning-related disorders remains unaccounted for. Perhaps the answer is not "hiding" exclusively in single, rare variants that remain yet to be identified, but also in gene × gene and higher-order chromatin interactions or epigenetic regulatory mechanisms and ways that the environment can determine the (epi)genome [156]. It is of note that epigenome-wide association studies have not been reported yet.