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Neuroimaging genetics studies of specific reading disability and developmental language disorder: A review

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Abstract

Developmental disorders of spoken and written language are heterogeneous in nature with impairments observed across various linguistic, cognitive, and sensorimotor domains. These disorders are also associated with characteristic patterns of atypical neural structure and function that are observable early in development, often before formal schooling begins. Established patterns of heritability point toward genetic contributions, and molecular genetics approaches have identified genes that play a role in these disorders. Still, identified genes account for only a limited portion of phenotypic variance in complex developmental disorders, described as the problem of "missing heritability." The characterization of intermediate phenotypes at the neural level may fill gaps in our understanding of heritability patterns in complex disorders, and the emerging field of neuroimaging genetics offers a promising approach to accomplish this goal. The neuroimaging genetics approach is gaining prevalence in language- and reading-related research as it is well-suited to incorporate behavior, genetics, and neurobiology into coherent etiological models of complex developmental disorders. Here, we review research applying the neuroimaging genetics approach to the study of specific reading disability (SRD) and developmental language disorder (DLD), much of which links genes with known neurodevelopmental function to functional and structural abnormalities in the brain.

1 | INTRODUCTION

Developmental disorders of spoken and written language are characterized by deficits in various linguistic domains such as reading, phonological processing, vocabulary, and grammatical skills (Hulme & Snowling, 2013), as well as atypical neural structure and function (Mayes, Reilly, & Morgan, 2015; Norton, Beach, & Gabrieli, 2015). A growing number of genes have been implicated in the etiology of these disorders, many of which play a role in neurodevelopmental processes such as neuronal migration, neurite outgrowth, cortical morphogenesis, and ciliary structure and function (Newbury, Monaco, & Paracchini, 2014). The developmental function of such genes is a likely source of neural anomalies, and the emerging field of neuroimaging genetics seeks to better understand the relationships among genetic and behavioral markers of disorders by establishing intermediate phenotypes at the neural level. Findings to date provide some compelling evidence for links among specific genes, brain structure and/or function, and reading- and language-associated phenotypes. Here, we review research employing a neuroimaging genetics approach to study specific reading disability (SRD) and developmental language disorder (DLD).[1] These disorders are of interest to study in parallel due to overlap in characteristic deficits, such as phonological processing, as well as shared neural and genetic underpinnings. We provide a brief introduction on genetic approaches to the study of complex disorders (please see Appendix A for explanation of technical concepts), along with an overview of each disorder and the related neuroimaging genetic findings reported thus far. Given the complex polygenic underpinnings of SRD and DLD, we have organized our discussion of the relevant imaging genetic findings by gene, beginning with coverage of well-established candidate genes for SRD and DLD and followed by those more recently associated with reading and/or language (genes investigated in relation to SRD and DLD using a neuroimaging genetic approach are listed in Table 1, and findings are summarized in Table 2). In addition, we only include genes that have been studied using a neuroimaging genetics approach. In order to present a clear account within the scope of neurodevelopmental disorders of spoken and written language, we have limited our review to studies including typically developing populations and populations with SRD or DLD and no additional neurological or psychiatric diagnosis.

2 | GENETICS IN DEVELOPMENTAL DISORDERS

The field of genetics took hold as a modern science following Mendel's foundational work in the mid-late 1800s and was furthered by a number of remarkable discoveries throughout the 20th century that led to the discovery of the genetic basis for many diseases. Following early genetic sequencing efforts in the 1970s and 1980s, the successful sequencing of the human genome was accomplished in 2003 (Human Genome Sequencing Consortium, 2004). This sequencing did not uncover a deterministic map of human traits and diseases but instead revealed a basic architecture from which complex interactions among genes, behavior, and environment dictate human ontogenesis (Gottlieb & Lickliter, 2007). Uncovering this architecture has paved the way for advances in analytic approaches for exploring the nature of gene–behavior relations. Previously, the primary method for uncovering the genetic underpinnings of particular traits was through linkage analysis. This technique allowed researchers to use genetic markers to identify the locations of the segment(s) of DNA in chromosomes that are shared by individuals within a family who exhibit a trait of interest (Smith, 1953). Linkage analysis is a useful tool for establishing inheritance in single-gene Mendelian disorders because it is based on deviations from expected patterns of inheritance and it traces cotransmission of a DNA marker allele and a disorder. For single-gene disorders, linkage can be identified by using

TABLE 1 Gene variants discussed in this review

Gene	Chr Location	Function	Imaging	Phenotype (language/reading)	References
BDNF	11p13	Neuronal survival Neuronal proliferation Synaptic growth	fMRI	Reading	Jasinska et al. (2016)
C2orf3/ GCFC2/ MRPL19	2p11-q11.2	Unknown	MRI DTI	Reading	Eicher et al. (2016) Scerri et al. (2012)
CMIP	16q23.2-q23.3	T-cell signaling	MRI	Reading	Skeide et al. (2016)
COL4A2	13q34	Type IV collagen subunit encoding	MRI	Reading	Skeide et al. (2016)
COMT	22q11.21	Dopamine metabolism	fMRI	Reading	Landi et al. (2013)
NRSN1	6p22.3	Neurite growth	MRI	Reading	Skeide et al. (2016)
ROBO1	3p12.3	Neuronal migration Axon guidance	MEG	Reading	Lamminmäki et al. (2012)
CCDC136/ FLNC	7q32.1	Unknown	MRI	Reading/Language	Gialluisi, Guadalupe, Francks, and Fisher (2017)
DCDC2	6p22	Neuronal migration Cilia	MRI fMRI rsMRI EEG DTI	Reading/Language	Cope et al. (2012) Czamara et al. (2011) Darki et al. (2012) Darki et al. (2014) Marino et al. (2014) Meda et al. (2008)
DYX1C1	15q21.3	Neuronal migration Cilia	MRI	Reading/Language	Darki et al. (2012) Darki et al. (2014)
FOXP2	7q31	Transcriptional regulation Neurogenesis	MRI fMRI PET	Reading/Language	Belton et al. (2003)

(Continues)

TABLE 1 (Continued)

Gene	Chr Location	Function	Imaging	Phenotype (language/reading)	References
					Liegois et al. (2003)
					Pinel et al. (2012)
					Skeide et al. (2016)
					Vargha-Kadem et al. (1998)
					Watkins et al. (2002)
					Wilcke et al. (2012)
KIAA0319	6p22	Neuronal migration	MRI fMRI rsMRI EEG DTI	Reading/Language	Czamara et al. (2011)
					Darki et al. (2012)
					Darki et al. (2014)
					Eicher et al. (2016)
					Pinel et al. (2012)
RBFOX2	22q12.3	Alternative exon splicing regulation	MRI	Reading/Language	Gialluisi et al. (2017)
SETBP1	18q12.3	DNA replication, apoptosis, transcription, nucleosome assembly	fMRI	Reading/Language	Perdue et al. (2019)
SLC2A3	4q32.1	Neural glucose transport regulation	EEG rsMRI DTI	Reading/Language	Roeske et al. (2011)
					Skeide et al. (2015)
ACOT13/ THEM2	6p22.3	Cell proliferation	MRI DTI	Reading/Language	Eicher et al. (2016)
					Pinel et al. (2012)
CNTNAP2	7q35	Cell adhesion Voltage-gated channels	MRI fMRI DTI	Language	Dennis et al. (2011)
					Koeda et al. (2015)
					Skeide et al. (2016)

(Continues)

TABLE 1 (Continued)

Gene	Chr Location	Function	Imaging	Phenotype (language/reading)	References
					Tan et al. (2010)
					Udden et al. (2017)
					Whalley et al. (2011)

Note. Publications focused on patient populations and/or individuals with disorders other than SRD and DLD were excluded from our review.

a few large family pedigrees; for the study of complex traits, the affected sib-pair linkage design which examines allele sharing for pairs of affected siblings in many different families is the most widely used linkage design (Plomin, DeFries, McClearn, & McGuffin, 2007). However, linkage approaches require a large gene effect for successful detection and thus have limited power for identification of genes of modest effect that contribute to complex traits and disorders (Risch & Merikangas, 1996). The vast majority of complex traits, conditions, and behaviors arise from the presence of multiple genetic variations or *polymorphisms* as well as gene-by-gene and gene-by-environment interactions. These include both common variants, which are present in greater than 1% of the genome, and rare variants, which occur in less than 1% of the genome. The most frequently occurring polymorphisms are single nucleotide polymorphisms (SNPs), in which there is a single base pair substitution in the structural units of DNA (The International SNP Map Working Group, 2001)—these represent approximately 90% of the variation in human DNA (The 1000 Genomes Project Consortium, 2011). Additional variation comes from insertion–deletion polymorphisms (indels) which affect one or more base pairs by the removal or addition of units (Weber et al., 2002) and copy number variations (CNVs) which represent alterations in the position or number of copies of larger sequences of DNA (Iafrate et al., 2004). SNPs and other common variants are of great scientific interest as markers of risk for genetic diseases or conditions in the general population because they occur relatively frequently and modest gene effects can be detected using association studies that do not require large family pedigrees.

Researchers who seek to understand the genetic origins of common diseases and traits are guided by two predominant hypotheses: the common disease/common variant (CDCV) hypothesis and the common disease/rare variant hypothesis (CDRV). According to CDCV, variants that are common in the population but have low penetrance (i.e., the probability that the carrier of the variant will express the disease) play a primary role in disease susceptibility (Lander, 1996; Reich & Lander, 2001; Schork, Murray, Frazer, & Topol, 2009). In contrast, CDRV suggests that rare variants with high penetrance are the major contributors to disease susceptibility (Schork et al., 2009). Evidence supports both of these models (Schork et al., 2009), and while ongoing research continues to contrast these models, a hybrid account for complex disease and trait susceptibility holds the most explanatory power. Consistent with the CDCV hypothesis, many of the identified genetic variants associated with SRD and DLD are (a) fairly common in the general population[2]; (b) carried by only a small subset of individuals with these disorders; and (c) not clearly linked to the behavioral phenotype of the individuals who carry them. There are, however, some rare variants associated with language and reading phenotypes which have been found in more severely impaired individuals,

TABLE 2 Summary of imaging geneticsfindings related to reading/language

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
BDNF	Jasinska et al. (2016)	**rs6265****	Continuous	fMRI	81	6–10	70 Caucasian 1 African-American 2 Hispanic 3 Asian 5 Mixed ethnicity	Increased activation bilaterally in Met carriers relative to Val/Val homozygotes	Val allele homozygotes performed better than Met carriers on passage comprehension, phonological memory, and IQ
C2ORF3/ MRPL19/ GCFC2	Eicher et al. (2016)	**rs2298948*** **rs917235***[⊥] **rs6732511***[⊥] [⊥]DYX3 locus upstream of *GCFC2* and *MRPL19*	Continuous	MRI DTI	332	3-20	European	Minor allele on rs2298948 associated with decreased CT and GMV. rs917235 associated with CT rs6732511 minor allele associated with increased GMV	NR
	Scerri et al. (2012)	**rs917235***** rs714939 rs1000585	Continuous	MRI DTI	76	6–25	98% European	G allele associated with reduced WMV	rs714939 and rs917235 associated with verbal IQ
CMIP	Skeide et al. (2016)	***rs12927866*** ***rs6564903*** ***rs3935802*** ***rs4265801*** ***rs16955705*** ***rs7201632*** **Joint SNP effect*****	Case/control	MRI	54	5–12	NR	*CMIP* related to bilateral portions of cerebellar WM	Associated with reading comprehension

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
COL4A2	Skeide et al. (2016)	**rs9521789**[*****]	Case/control	MRI	54	5–12	NR	Related to cerebellar GMV	No significant associations reported
COMT	Landi et al. (2013)	**rs4680**[****]	Case/control	fMRI	86	6–10	83 Caucasian 3 African-American	Greater activation in left hemisphere reading-related regions for Met carriers	Significant differences between genotype groups in phonological awareness (PA) and spelling
NRSN1	Skeide et al. (2016)	***rs9356928*** ***rs4285310*** ***rs3178*** **Joint SNP effect**[*****]	Case/control	MRI	54	5–12	NR	Joint SNP association with GMV and WMV	*NRSN1* associated with reading comprehension performance. GMV in VWFA ROI related to *NRSN1* predicted reading outcomes
ROBO1	Lamminmäki et al. (2012)	N/A	Case/control	MEG	10	19–51	Finnish	Ipsilateral auditory suppression in both hemispheres related to *ROBO1* expression levels	NR
CCDC136/ FLNC	Gialluisi, Guadalupe, Francks, and Fisher (2017)	rs59197085 **rs56184882**[**] **rs339054**[**] **rs339046**[**]	Continuous	MRI	1275	18–35	NR	Associated with cortical surface area in IFG	NR
DCDC2	Cope et al. (2012)	rs793862 rs807701 rs807724	Continuous	fMRI	82	7–12	European American	*DCDC2* variants associated with activation during	Nominally significant associations between *DCDC2* variants and

(Continues)

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
		BV677278 STR[**] BV677278 del. rs1087266						print and auditory processing Nominal associations between *DCDC2* variants and activation during word reading and nonword reading tasks	measures of IQ, PA, word reading, and passage comprehension
	Czamara et al. (2011)	**Chr6:24459391/ rs1052724905**[**] **Chr6:24564881**[**] **Chr6:24571041**[**] **Chr6:24581378/ rs1033367480**[**]	SRD	EEG	200	8–19	German	Four rare variants on *DCDC2* or between *DCDC2* and *KIAA0319* were associated with late mismatch negativity (MMN) to speech	NR
	Darki et al. (2012)	**rs793842**[*****] rs793862 rs807701 rs2328819 rs2792682 rs7751169 rs9460974	Continuous	MRI DTI	76	6–25	98% European	Associated with WMV	Positive correlation between white matter volume and reading scores. No direct relationships between SNPs and behavior.
	Darki et al. (2014)	**rs793842**[*****]	Continuous	MRI DTI	76	6–25	98% European	Associated with WMV in left temporo-parietal region and with	Associated with reading comprehension scores; WMV and CT

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
								CT in left temporo-parietal and occipital cortices	correlated with reading scores
DCDC2	Eicher et al. (2016)	rs707864	Continuous	MRI DTI	332	3–20	European	NS	NR
	Marino et al. (2014)	***DCDC2*-intron2 deletion****	Case/control	DTI	47	16–21	NR	Reduced WM integrity in subjects with *DCDC2* intron2 deletion	Positive correlation between fractional anisotropy (FA) and average reading scores
	Meda et al. (2008)	***DCDC2*-intron2 deletion***	Continuous	MRI	56	19–85	NR	Increased GMV in carriers of *DCDC2* intron 2 deletion compared to those homozygous for no deletion	NR
DYX1C1	Darki et al. (2012)	**rs3743204**[****] rs3743205 rs17819126	Continuous	MRI DTI	76	6–25	98% European	Associated with WMV in bilateral temporo-parietal region	Significant correlation between WMV and reading scores
	Darki et al. (2014)	**rs3743204**[*****]	Continuous	MRI DTI	76	6–25	98% European	Associated with bilateral temporo-parietal WMV, replicating	Significant correlation between WMV and reading scores

(Continues)

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
								findings of Darki et al. (2012) across an additional time point	
FOXP2	Belton et al. (2003)	KE Family***	Case/control	MRI	34	9–27	European	Altered GM density in affected family members	NR
	Liegois et al. (2003)	KE Family***	Case/control	fMRI	20	19–56	European	Affected family members showed an atypical pattern of activation in a verb generation task compared to unaffected family members and controls	NR
FOXP2	Pinel et al. (2012)	**rs10249234***** **rs7784315***** **rs7812028*** **rs17137135***** **rs6980093***** rs6942634 rs2894699 rs1476535 rs10255943 rs10486026 rs10261780 rs10262103	Continuous	fMRI	94	*M* = 24.7	European	Associations with activation during a sentence reading task	NR

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
		rs4727799 rs17312686 rs2106900 rs17312861 rs12113612 rs10266297 rs10279936 rs7799109 rs12532920 rs17137124 rs10269986 rs1229761 rs1229758 rs12705966 rs10230087 rs7782412 rs1456029 rs12670585 rs6966051 rs17213159 rs1378771 rs12705971 rs12705973 rs2396766 rs12671330							
FOXP2	Skeide et al. (2016)	***rs923875*** ***rs12533005*** ***rs6980093*** ***rs10230558***	Continuous	MRI	54	5–12	NR	Joint SNP effect related to GMV in left medial	NS

(Continues)

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
		rs7782412 ***rs936146*** **Joint SNP effect**[*****]						superior frontal gyrus	
	Vargha-Kadem et al. (1998)	KE Family[***]	Case/control	PET MRI	34	NR	European	Atypical activation during a word repetition task in affected family members. Regional alterations in GM structure	Affected family members show deficits in word repetition, nonword repetition, and simultaneous and sequential orofacial movements
	Watkins et al. (2002)	KE Family[***]	Case/control	MRI	34	9–27	European	Atypical pattern of GMV in affected family members compared to unaffected family members and controls	Correlation between caudate nucleus volume and performance on test of oral praxis, nonword repetition, and coding subtest of Wechsler Intelligence Scale in affected family members
	Wilcke et al. (2012)	**rs12533005**[**]	Case/control	fMRI	33	*M* = 11	German	Decreased activation in risk allele carriers during rhyme decision task	NR
	Darki et al. (2012)	**rs6935076**[*****] rs4504469	Continuous	MRI DTI	76	6–25	98% European		Positive correlations between WMV and

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
		rs2143340						Associated with left temporoparietal WMV	reading comprehension and WMV and timed single-word reading; No significant correlations between SNPs and reading
KIAA0319	Darki et al. (2014)	**rs6935076**[*****]	Continuous	MRI DTI	76	6–25	98% European	Associated with bilateral temporoparietal WMV, replicating findings from Darki et al. (2012) across an additional time point	Significant correlation between WMV and reading scores
	Eicher et al. (2016)	**rs9461045**[******] rs9295626 rs10456309 rs4576240	Continuous	MRI DTI	332	3–20	European	Associated with cortical thickness and WM integrity	NR
	Pinel et al., 2012	rs2235676 rs9467247 rs3756821	Continuous	fMRI	94	$M = 24.7$	Primarily Caucasian	NS	NR
RBFOX2	Gialluisi et al. (2017)	**rs5995177**[***] **rs78563107**[***] **rs6000084**[***] **rs6000085**[***] **rs144006011**[***]	Continuous	MRI	1275	18–35	NR	Associated with cortical thickness	NR

(Continues)

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
SETBP1	Perdue et al. (2019)	**rs7230525**[***]	Continuous	fMRI	73	5–12	116 Caucasian 2 African American 3 Hispanic 4 Asian 8 mixed 2 unreported	Interaction between genotype, lexicality and modality in the right inferior parietal lobule	Genotype associated with phonological working memory
SLC2A3	Roeske et al. (2011)	**rs4234898**[***] **rs11100040**[***]	SRD	EEG	200 18 6[c***]	8–19	German	Altered late MMN response	NR
	Skeide et al. (2015)	rs4234898 **rs11100040**[***]	Continuous	rsfMRI DTI	34	9–12	NR	Weaker functional and structural connectivity in risk allele carriers	WM integrity related to PA performance
THEM2/ ACOT13	Eicher et al. (2016)	**rs3777663***	Continuous	MRI DTI	332	3–20	European	Associated with cortical thickness	NR
	Pinel et al. (2012)	**rs17243157**[***] rs3756819 rs1061925 rs3181227 rs2223588 rs6928074 rs9461049 rs926529 rs1885211	Continuous	fMRI	94	*M* = 24.7	Primarily Caucasian	Associated with functional asymmetry during reading and speech listening tasks	NR
CNTNAP2	Dennis et al. (2011)	**rs2710102**[***]	Continuous	DTI	328	*M* = 23.4	Caucasian	Atypical structural connectivity	NR

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	*N*[a]	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
								indices in risk allele carriers	
	Koeda et al. (2015)	**rs7794745**[***] rs2710102	Continuous	fMRI	108	*M* = 26.3	Japanese	Genotype group differences in activation during general auditory processing, human voice processing, and language processing	NS
	Skeide et al. (2016)	***rs7794745*** ***rs10246256*** ***rs2710102*** ***rs759178*** ***rs17236239*** ***rs4431523*** ***rs2710117*** **Joint SNP effect**[*****]	Continuous	MRI	54	5–12	NR	Joint SNP effect related to WMV in left cerebral and cerebellar peduncles	Association with reading comprehension
CNTNAP2	Tan et al. (2010)	**rs7794745**[***]	Continuous	MRI DTI	114	NR	NR	Reduced GMV, WMV, and WM integrity in risk allele homozygotes	NR
	Udden et al. (2017)	**rs7794745**[****]	Continuous	MRI	1717	*M* = 24.3	Primarily European Caucasian	Reduced GMV in AT/TT carriers compared to AA homozygotes	NR

(Continues)

TABLE 2 (Continued)

Gene	Reference(s)	Variant(s)	Design	Imaging	N^a	Age[a,b]	Ethnic Background[a]	Imaging findings	Behavioral findings
	Whalley et al. (2011)	**rs7794745**[***] **rs2710102**[***]	Continuous	fMRI	66	$M = 20.5$	Caucasian	Atypical patterns of activation in risk allele carriers during sentence completion task	NS

Note. Shading indicates relevant phenotype: white = reading, light gray = reading and/or language, dark gray = language. Boldface indicates SNPs for which significant imaging-genetic results were reported. For studies that included corrected and uncorrected *p* values, asterisks indicate corrected *p* to be consistent with other studies presented here.

Abbreviations: CT, cortical thickness; GMV, gray matter volume; NR, not reported; NS, no significant findings; WMV, white matter volume.

[*] $p < .01$, uncorrected.

[**] $p < .001$, uncorrected.

[***] $p < .05$, corrected.

[****] $p < .01$, corrected.

[*****] $p < .001$, corrected.

[a]Information listed refers to samples included in neuroimaging analyses.

[b]Age ranges or means reported according to information available in each study.

[c]Replication sample.

including some of the *FOXP2* variants associated with speech and language impairment (e.g., see Estruch et al., 2016).

Under both the CDRV and CDCV approaches, two primary methods are used for the identification of genes associated with complex neurodevelopmental disorders. Hypothesis-driven candidate gene association studies investigating specific SNPs allow researchers to identify how alleles at one or more pre-identified locations on the gene are related to specific phenotypes (Kornilov & Grigorenko, 2016). Alternatively, an exploratory approach may be taken using a genome-wide association study (GWAS) to identify SNPs associated with a trait of interest; this approach is especially useful for detection of new variants (Hirschhorn & Daly, 2005). GWAS is a powerful tool, but it is costly and effortful to genotype thousands of SNPs per individual, and GWAS requires large sample sizes for sufficient power to detect small effects associated with complex traits (Hirschhorn & Daly, 2005). Recent efforts to build and share large genetic databases (e.g. the Pediatric Imaging, Neurocognition, and Genetics [PING] Data Repository; Jernigan et al., 2016) aim to reduce the burden and increase power of GWAS studies. The field of neuroimaging genetics applies these genetic methods in combination with neuroimaging techniques to improve characterization of complex traits through the identification of intermediate phenotypes that link genes to behaviors through neural mechanisms. Using these methods, geneticists, neuroscientists, and psychologists may work together to deepen the understanding of complex developmental disorders such as specific reading disability (SRD) and developmental language disorder (DLD) in a step to improve identification and treatment of these conditions.

3 | SPECIFIC READING DISABILITY

Specific reading disability (SRD), or developmental dyslexia (DD), is a prevalent learning disability affecting around 7–16% of school-age children and is characterized by deficits in accurate and/or fluent word recognition, decoding and spelling which do not result from inadequate educational experiences (Fletcher, 2009; Lyon, Shaywitz, & Shaywitz, 2003; Pennington & Bishop, 2009). SRD is neurobiological in origin, and functional and structural magnetic resonance imaging (fMRI/MRI) reveal atypical brain characteristics (in both structure and function) associated with SRD in left temporo-parietal, occipito-temporal, and inferior frontal regions (e.g., Landi et al., 2010 Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Pugh et al., 2001; Richlan, Kronbichler, & Wimmer, 2009, 2013). Specifically, individuals with SRD exhibit reduced activation during reading and phonological awareness tasks relative to controls in left temporo-parietal and occipito-temporal regions (e.g., Richlan et al., 2009). Mixed findings of over- and under-activation in the left inferior frontal cortex in SRD suggests that activation in this area may be task-specific and warrants further investigation (e.g., Richlan et al., 2009). Reports of anomalous cortical structure in SRD include reduced gray matter volume in bilateral superior temporal regions (Hoeft et al., 2007; Richlan et al., 2013), bilateral temporo-parietal regions and insula (Hoeft et al., 2007), bilateral occipito-temporal and right temporo-parietal regions (Kronbichler et al., 2008), and atypical sulcal pattern in left temporo-parietal and occipito-temporal regions (Im, Raschle, Smith, Grant, & Gaab, 2016). Advances in the use of diffusion-weighted MRI (including diffusion tensor imaging, or DTI) allow examination of white matter microstructure, indexed by a measure of white matter integrity called fractional anisotropy (FA), and measures of diffusivity along white matter tracts: mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). The application of diffusion-weighted MRI to the study of SRD has shown decreased white matter integrity (reduced FA) in left hemisphere

tracts including the arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corona radiata, which structurally link language-related cortical areas (Vandermosten, Boets, Wouters, & Ghesquière, 2012; Yeatman et al., 2011). Although some of the observed neurobiological alterations in SRD may be a result of reading difficulties, much of the altered brain function and structure characteristic of SRD is observed in pre-reading children and consequently has been proposed to be rooted in underlying genetic risk factors (Ozernov-Palchik & Gaab, 2016).

3.1 | Neuroimaging genetics studies of specific reading disability

3.1.1 | SRD candidate genes: *DCDC2*, *KIAA0319*, *THEM2*, *NRSN1*, *DYX1C1*, and *ROBO1*

Variation on *DCDC2* has been associated with performance on several measures of reading and reading-related skills including phonological skills, word/pseudoword reading, and spelling in samples with SRD (Chen, Zhao, Zhang, & Zuo, 2017; Ludwig, Roeske, et al., 2008; Marino et al., 2012; Matsson et al., 2015; Meng et al., 2005; Wilcke et al., 2009) and without SRD (Lind et al., 2010; Newbury et al., 2011; Powers et al., 2013; Scerri et al., 2011; Sun et al., 2014; Venkatesh, Siddaiah, Padakannaya, & Ramachandra, 2013; Zhang et al., 2016). Extant research suggests that variation in this gene is associated with subtle cortical malformations in brain areas important for reading (Meng et al., 2005). For example, in a study of typically developing Swedish-speaking children and young adults, one SNP in *DCDC2* (rs793842[3]) was related to white matter volume in left temporo-parietal cortex, with the highest white matter volume indices in CC homozygotes and lowest in TT homozygotes, and heterozygotes falling in between (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012). In addition, the authors found a significant positive correlation between white matter volume and reading fluency; however, no direct associations between SNPs and behavioral performance were significant (Darki et al., 2012). The association between rs793842 and left temporo-parietal white matter volume was replicated in a follow-up analysis that examined the same sample with the inclusion of a third longitudinal time point, and a significant association between this SNP and cortical thickness in the left temporo-parietal and occipital cortices emerged in this follow-up analysis, such that T-allele carriers had thicker cortex in these regions (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2014). Additionally, rs793842 was associated with reading comprehension scores.

A second polymorphism in *DCDC2*, a deletion in intron 2 (hereafter, *DCDC2d*), which encompasses BV677278, has been associated with SRD, and with interindividual variation reading performance and motion perception in children with SRD and typical development (TD; Brkanac et al., 2007; Cicchini, Marino, Mascheretti, Perani, & Morrone, 2015; Gori et al., 2015; Harold et al., 2006; Ludwig, Schumacher, et al., 2008; Marino et al., 2012; Meng et al., 2005; Wilcke et al., 2009).[4] One imaging genetics study of the *DCDC2d* reports significantly increased gray matter volume in a number of regions related to language and reading, including bilateral temporo-parietal regions, in typically developing individuals heterozygous for *DCDC2d* (Meda et al., 2008). Moreover, a study of white matter microstructure in individuals with and without SRD found the *DCDC2d* to be associated with reduced white matter integrity in the left arcuate fasciculus and the posterior corpus callosum, regardless of reading impairment status. Within the reading impaired group, white matter integrity was reduced bilaterally in the inferior longitudinal fasciculus and anterior corpus callosum in those with the deletion relative to those without (Marino et al., 2014). Marino et al. (2014) also reported positive correlations between white matter integrity and average reading scores in several left-hemisphere tracts related to reading and language.

In addition to structural findings, recent fMRI and event-related potential (ERP) studies that engage the neural circuitry for reading and language provide evidence for links between *DCDC2* and brain function. One ERP of particular interest in reading and language research is the mismatch negativity (MMN) response, a commonly used index of auditory discrimination (typically of tones or phonemes) that is characteristically reduced in individuals with reading and language impairment (Schulte-Körne, Deimel, Bartling, & Remschmidt, 2001). Czamara et al. (2011) reported an attenuated late MMN response to phonemic stimuli in minor allele carriers of one SNP in *DCDC2* (chr6:24459391/rs1052724905) and three locations between *DCDC2* and *KIAA0319* (chr6:24564881, chr6:24571041, and chr6:24581378/rs1033367480) in a sample of children with SRD. Further, using fMRI, Cope et al. (2012) identified patterns of activation associated with alleles of BV677278 during a set of language and reading tasks and replicated previous findings of gene/reading behavioral associations. Specifically, BV677278 alleles were significantly associated with activation in the left temporo-parietal cortex (positive correlation) and the right occipito-temporal gyrus (negative correlation) during processing of printed words and negatively associated with activation in the right occipito-temporal gyrus during processing of spoken words, indicating relevance of this gene for both written and spoken language. The functional association in the temporo-parietal cortex is consistent with the localization of structural associations with *DCDC2d* discussed above (Meda et al., 2008), and together, these results link *DCDC2* and temporo-parietal anomalies that are characteristic of SRD.

A close neighbor of *DCDC2* within the same locus on chromosome 6p22.3, *KIAA0319*, is another well-studied candidate gene for SRD that has been associated with reading ability within SRD (Cope et al., 2005; Couto et al., 2010; Dennis et al., 2009; Ludwig, Roeske, et al., 2008; Mascheretti et al., 2014) and the general population (Lim, Wong, Ho, & Waye, 2014; Luciano et al., 2007; Newbury et al., 2011; Paracchini et al., 2008; Scerri et al., 2011; Venkatesh et al., 2013; Sun et al., 2014). Animal research shows that the expression pattern of *KIAA0319* in the developing brain is consistent with its hypothesized role in neuronal migration, and recent bioinformatics analysis has suggested its involvement in additional neurodevelopmental and signaling functions (Peschansky et al., 2010; Poon et al., 2011; Szalkowski et al., 2013, 2012; Velayos-Baeza, Levecque, Kobayashi, Holloway, & Monaco, 2010). Consistent with *KIAA0319*'s hypothesized role from animal findings, structural associations with *KIAA0319* have been reported in human MRI research. An association between white matter volume in the left temporo-parietal region and *KIAA0319* SNP rs6935076 has been identified (Darki et al., 2012) and replicated with an additional right hemisphere effect when data from a third longitudinal time point were added to the analysis (Darki et al., 2014). Furthermore, Eicher et al. (2016) reported decreased cortical thickness in a left orbitofrontal region in carriers of the minor allele of the SNP rs9461045 (associated with single-word reading and spelling ability; Dennis et al., 2009) relative to those homozygous for the major allele within a sample of individuals ages 3–20 years from the Pediatrics Imaging Neurocognition Genetics study (PING) database.[5] With regard to structural connectivity, the minor allele of the same SNP was associated with reduced white matter integrity in the corpus callosum. These findings point toward an effect of *KIAA0319* on language-related brain structures that may underlie individual differences in language and reading abilities.

In addition to *DCDC2* and *KIAA0319*, two additional genes within 6p22-21.3 (*THEM2* and *NRSN1*) have been linked with reading-associated neural structure and/or function across multiple studies. Presence of the minor allele at rs3777663 in *THEM2* (also known as *ACOT13* and previously identified as a protective allele [Eicher et al., 2014]) has been linked to increased cortical thickness in the left inferior frontal region (Eicher et al., 2016). In a separate study, Pinel et al. (2012) found that

THEM2 SNP rs17243157 was associated with functional asymmetry in a posterior temporal region during reading and speech listening tasks, with a stronger effect for reading.

NRSN1 has recently been implicated in reading-related cortical structure. Specifically, recent work has identified associations between variation on *NRSN1* and gray matter volume in right parieto-occipital, left lateral occipital, and left occipito-temporal regions, as well as white matter volume in a left postcentral region (Skeide et al., 2016). In a follow-up classification analysis, left occipito-temporal volume performed significantly above chance in classifying subjects into SRD and control groups, and variation on *NRSN1* was further associated with reading comprehension (Skeide et al., 2016). These structural and functional associations may be attributed to variation in *NRSN1* expression, which has been linked to axon and dendrite growth (Araki et al., 2002). Together, these findings support *THEM2* and *NRSN1* as loci for further investigation of links between genes, neural structure/function, and reading.

The remaining candidate genes for SRD have received relatively little attention in human neuroimaging studies. Like those of other SRD candidate genes, the protein encoded by *DYX1C1* has been linked to neurodevelopmental processes (Currier, Etchegaray, Haight, Galaburda, & Rosen, 2011; Rosen et al., 2007; Szalkowski et al., 2011; Tammimies et al., 2016; Tarkar et al., 2013; Threlkeld et al., 2007; Wang et al., 2006), and variation on this gene has been associated with reading and spelling abilities in both general population (Bates et al., 2010; Newbury et al., 2011; Zhang et al., 2012) and clinical samples (Lim, Ho, Chou, & Waye, 2011; Marino et al., 2007; Venkatesh, Siddaiah, Padakannaya, & Ramachandra, 2014). With respect to neuroimaging, Darki et al. (2012) found a relationship between SNP rs3743204 in *DYX1C1* and white matter volume in bilateral temporo-parietal regions and correlations between white matter volume in these regions and reading scores. As with the *KIAA0319* findings described above, these findings were replicated when a third longitudinal time point was added for the same sample (Darki et al., 2014).

ROBO1 appears to serve an axon guidance function that regulates the connections between brain hemispheres and between cortical and subcortical structures (Andrews et al., 2006; Hannula-Jouppi et al., 2005; Massinen et al., 2016; Whitford et al., 2002). Linkage studies suggest that this gene is related to SRD (Fisher et al., 2002; Mascheretti et al., 2014; Nopola-Hemmi et al., 2001; Tran et al., 2014) and speech-sound disorder (Stein et al., 2004), and research in the general population indicates an association with phonological skills (Bates et al., 2011). In the context of neuroimaging, *ROBO1* has been investigated in one study that employed magnetoencephalography (MEG) to examine auditory processing in individuals with reading impairment from a family carrying a rare, weakly expressing haplotype of the *ROBO1* gene relative to typical controls (Lamminmäki, Massinen, Nopola-Hemmi, Kere, & Hari, 2012). Ipsilateral auditory suppression in both hemispheres was related to *ROBO1* expression levels in the haplotype carrier group, and these subjects showed significantly weaker ipsilateral suppression compared to the control group. These imaging findings point toward a possible auditory processing deficit as the source of previously observed associations between *ROBO1*, phonological skills, and speech-sound disorders.

3.1.2 | Summary: Neuroimaging genetics studies of SRD

The early observation of heritability in SRD and subsequent identification of candidate genes have made SRD a model for studying genetic contributions to complex cognitive traits and understanding the genetic bases of heterogeneous neurodevelopmental disorders. Further, the extensive research on neural structure and function in SRD provides a basis for linking genes, brain structure and function, and behavior in this disorder. Associations between SRD risk genes and gray

and white matter structure in reading-associated regions are consistent with the role of these genes in brain development and further support atypical neural development as a contributing factor to reading difficulties. Although cross-report comparisons of structural findings are mixed, inconsistencies are at least partially due to variability in SNPs investigated for a particular gene, the structural metrics that are used, ages of participants, and inclusion of individuals with SRD vs. use of a broader population sample. Additional research, including replication studies, is needed to clarify these ambiguities and more definitively establish links among specific genes and polymorphisms, and neural structure. While association among genetic variation and neural function is less well studied in SRD, extant fMRI and ERP studies linking polymorphisms on candidate genes to well-characterized auditory electrophysiological components and atypical neural function in reading-related regions provide some encouraging evidence for mapping of gene–brain–behavior relations.

4 | DEVELOPMENTAL LANGUAGE DISORDER

Developmental language disorder (DLD) refers to difficulties in language acquisition that may affect comprehension and/or production of language across modalities (e.g., spoken and written; American Psychological Association, 2013). Because DLD often affects components of language that are also impaired in SRD, such as phonological awareness, similarities in the neural and genetic underpinnings of these two disorders are expected. The neurobiology of DLD has not been as well studied as that of SRD, but a small body of literature indicates decreased activation during language processing tasks (broadly construed) in individuals with DLD relative to typical controls in temporo-parietal and superior and middle temporal regions, as well as some mixed evidence for atypical functioning in the left inferior frontal gyrus (de Guibert et al., 2011; Hugdahl et al., 2004; Mayes et al., 2015). A number of genes have been linked to impairments in speech and language function, including *FOXP2*, *CNTNAP2*, *ATP2C2*, and *CMIP* (Newbury, Fisher, & Monaco, 2010). Because these genes play potentially wide-reaching roles in neurodevelopment and brain function (discussed below), imaging genetic research on these DLD-associated genes is not only helpful for linking genes to their specific neural functions in the context of expressive and receptive language but may also be helpful for understanding the potential cascading effects of these genes on reading.

4.1 | Neuroimaging genetics studies of developmental language disorder

4.1.1 | *FOXP2*

FOXP2 was first linked to language impairment in the KE family, which gained the attention of geneticists because half of the members are affected by a severe inherited speech and language disorder (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). Genetic associations with this speech and language disorder have been extensively investigated in a three-generation pedigree of the KE family that includes 27 family members (Lai et al., 2001). More recently, *FOXP2* has been linked to variability in language and reading traits in both the general population and in a clinical sample (Mozzi et al., 2017). Using linkage analyses, researchers first identified the locus associated with inheritance of the disorder (SPCH1, chromosome 7q31), and later determined that a mutation in the gene *FOXP2* was causally related to the disorder (Fisher et al., 1998; Lai et al., 2001). *FOXP2* belongs to a family of genes that

produce proteins that regulate expression of other genes during neurodevelopmental processes (Carlsson & Mahlapuu, 2002), leading to complex and widespread contribution of this gene to neurodevelopment (Newbury et al., 2010).

Among the series of studies investigating the nature of the KE family's impairment are several examinations of neural structure and function. Studies of gray matter structure in the KE family have revealed atypical gray matter volume and density in affected compared to unaffected family members in cortical and subcortical regions associated with motor and language functions including the inferior frontal gyrus, pre-supplementary motor area, caudate nucleus, and cerebellum (Belton, Salmond, Watkins, Vargha-Khadem, & Gadian, 2003; Vargha-Khadem et al., 1998; Watkins et al., 2002). These early findings point toward a relationship of *FOXP2* with brain structure in regions related to speech production and language; however, additional studies are needed to confirm whether these patterns hold in members of the general population who exhibit atypical expression of *FOXP2*.

In addition to structural anomalies, affected members of the KE family have shown altered functional neural activation during both overt and covert language production tasks in motor areas and language-related regions (Liegeois et al., 2003; Vargha-Khadem et al., 1998). Research in the KE family has also led to the investigation of functional associations with *FOXP2* SNPs in the general population, with consistent findings related to activation in the left inferior frontal cortex (Pinel et al., 2012; Wilcke et al., 2012). For example, associations have been observed between rs6980093 and left inferior frontal activation and between rs7784315 and rs17137135 and left precentral activation in response to sentences presented in auditory and visual modalities in a study of typically developing young adults (Pinel et al., 2012). Moreover, Wilcke et al. (2012) included typically developing children and children with SRD in their fMRI study of *FOXP2* SNPs. Results revealed decreased activation during a rhyme decision task in the temporo-parietal cortex, inferior frontal cortex, superior occipital gyrus, and lingual gyrus in carriers of the risk allele on rs1253305 (Wilcke et al., 2012). This evidence suggests that the neural alterations associated with *FOXP2* are not limited to the mutation characteristic of the KE family, but may play a role in language disorders more broadly with possible implications for reading impairment.

4.1.2 | *CNTNAP2*

CNTNAP2 has been identified as a risk-gene for DLD and autism (Alarcón et al., 2008; Strauss et al., 2006), and variation in *CNTNAP2* has been associated with performance on nonsense word repetition (Vernes et al., 2008) and with rapid auditory processing (Riva et al., 2018). *CNTNAP2* (also known as *CASPR2*), a gene proximal to and regulated by *FOXP2*, is involved in regulation of neuron–glia interaction related to myelination and localization of ion channels (Poliak et al., 2003; Rasband, 2004; Vernes et al., 2008). These functions have been taken as support for a role of this gene in structural connectivity and neural activity. Functional neuroimaging studies implicate a relationship between *CNTNAP2* polymorphisms and atypical lateralization of language processing. For example, Whalley et al. (2011) found associations between lateralization for language and two *CNTNAP2* polymorphisms in typically developing adults during a sentence completion task. Specifically, increased activation in the right inferior frontal cortex combined with decreased activation in the left superior parietal lobule was observed in individuals homozygous for the risk allele at rs2710102 compared to all other subjects; and increased activation in the right middle temporal gyrus was observed in those homozygous for risk allele at rs7794745 compared to all other subjects. Further evidence for atypical lateralization for language associated with *CNTNAP2*

polymorphisms comes from a study of language, voice, and general auditory processing. Koeda et al. (2015) reported increased activation in the right middle frontal gyrus during native language listening in Japanese carriers of the nondominant allele for rs7794745. This pattern of increased right hemisphere activation also held for human voice perception (reversed sentences) the right middle frontal gyrus. Further, these authors observed an interaction between lateralization of function during voice processing (forward and reversed speech), rs7794745 genotype, and handedness, suggesting a complex influence of this SNP on voice processing networks in relation to handedness and lateralization.[6]

With respect to brain structure, two studies have identified regional reductions in gray matter volume associated with the risk allele on rs7794745 primarily affecting occipital, fusiform, and cerebellar regions (Tan, Doke, Ashburner, Wood, & Frackowiak, 2010; Uddén, Snijders, Fisher, & Hagoort, 2017). Additionally, altered white matter structure associated with *CNTNAP2* has been reported in fronto-occipital and thalamic tracts (Tan et al., 2010) as well as midbrain tracts that facilitate communication among the cortex, cerebellum, and other central nervous system structures (Skeide et al., 2016). Using diffusion MRI, Dennis et al. (2011) identified a pattern of white matter structure characterized by local rather than long-range connections in individuals homozygous for the risk allele on *CNTNAP2* SNP rs2710102. These reductions in long-range connectivity may indicate a weakened link between frontal and temporal cortical regions important for language processing and production. These white matter findings are consistent with *CNTNAP2*'s role in myelination and suggest that *CNTNAP2* may contribute to variation in language skills via modulation of connectivity among regions that are needed for effective language function.

4.1.3 | Summary: Neuroimaging genetics studies of DLD

Neuroimaging genetic investigations of these two primary DLD candidate genes suggest specific roles of each gene in language-related neural function. Imaging genetics studies of *FOXP2* indicate that this gene affects brain regions associated with language production and speech motor planning (Liegeois et al., 2003; Pinel et al., 2012; Vargha-Khadem, Gadian, Copp, & Mishkin, 2005), with preliminary links to activity in posterior language regions (Wilcke et al., 2012). *CNTNAP2* has also been found to have effects on functional activation in language-related regions, including inferior frontal and middle temporal gyri (Whalley et al., 2011) and on gray matter morphology in occipital, fusiform, and cerebellar regions (Tan et al., 2010; Uddén et al., 2017); in addition, this gene has effects on structural and functional connectivity among language-associated regions and more domain general regions (Dennis et al., 2011; Skeide et al., 2016). The compelling neuroimaging genetic findings related to both of these genes may direct future research to further characterize their roles in DLD. Further examination of *FOXP2* in the general population will be particularly useful to disentangle the specific effects of the KE Family mutation from more common polymorphisms that may contribute to individual differences in language abilities. Additional functional neuroimaging research is needed to clarify the associations of these genes with specific aspects of language processing. Furthermore, several additional DLD candidate genes (e.g., *ATP2C2* and *CMIP*) have yet to be studied using neuroimaging genetics, and this approach may provide insight into the mechanisms by which they impact language function.

5 | ADDITIONAL GENES LINKED TO READING AND LANGUAGE

Neuroimaging genetic research provides an informative approach to understanding the contributions of novel candidate genes for SRD and DLD and language/reading-related polymorphisms located in intergenic regions. Gialluisi et al. (2017) reported promising findings in several recently identified candidate genes for reading and language disorders. The minor allele of *RBFOX2* SNP rs5995177, previously linked to reading/language skills (Gialluisi et al., 2014), was significantly associated with decreased cortical thickness in parietal, temporal, and inferior frontal regions of interest (Gialluisi et al., 2017). Furthermore, three SNPs located upstream of *CCDC136* (rs56184882, rs339054, and rs339046) were nominally related to cortical surface area of the inferior frontal gyrus bilaterally (Gialluisi et al., 2017). Evidence for the role of a set of SNPs located in a noncoding region has also been revealed by neurogenetic methods. Variation on a haplotype formed by rs4234898 and rs11100040 in a noncoding region in chromosome 4q32.1 has been associated with the MMN response in children with SRD (Roeske et al., 2011). Both SNPs were associated with regulation of the glucose transport gene *SLC2A3*, leading the authors to propose that the attenuated MMN response observed in children with SRD may arise from reduced glucose resulting from the modulation of *SLC2A3* expression by rs4234898 and rs11100040. In another investigation, Skeide et al. (2015) reported reduced functional and structural connectivity among left hemisphere reading/language regions in children carrying the risk-allele at rs11100040. Additional research will be needed to investigate a potential causal mechanism among these SNPs, regulation of *SLC2A3*, connectivity, and reading and language abilities.

Several studies have linked the *DYX3* genetic locus on chromosome 2 containing *GCFC2/C2Orf3* and *MRPL19* to SRD (Anthoni et al., 2007; Fagerheim et al., 1999; Kaminen et al., 2003), but the role of these genes in neural function remains unknown. Two neuroimaging genetic studies of this locus suggest associations with neural structure. Eicher et al. (2016) reported suggestive associations between gray matter structure and SNPs in and upstream of *GCFC2*. A separate study linked one *DYX3* SNP to decreased white matter volume in the posterior corpus callosum and cingulum, suggesting a disturbance in interhemispheric connectivity between posterior reading-related regions (Scerri et al., 2012). Scerri and colleagues also found an association between variation in DYX3 SNPs and verbal IQ performance, extending previous links of the DYX3 locus with reading to a broader cognitive scope.

Our laboratory has recently conducted a behavioral association and neuroimaging genetic study of the *SETBP1* gene, which was previously associated with expressive language function in an isolated population in Russia with a high prevalence of DLD (Kornilov et al., 2016). This population is of interest for investigating a shared genetic cause of DLD because its remote location leads to reduced genetic diversity and increased heritability of traits within the population. A follow-up study revealed a significant association between the *SETBP1* gene and reading-relevant skills (e.g., phonological working memory) in a group of typically developing children in the United States (Perdue et al., 2019). Further, we investigated brain activation for the SNP with the strongest association (rs7230525) in a subset of participants who completed an fMRI task that involved reading and listening to words and pseudowords. Our imaging analysis revealed a complex three-way interaction among genotype, word type, and presentation modality in the right inferior parietal lobule. Breaking down this interaction revealed greater activation for more difficult to process printed stimuli (pseudowords > words) for individuals in the genotype group associated with poorer phonological

skills (Perdue et al., 2019). Although preliminary, these findings point to a relation between variability in *SETBP1* and the role of attentional networks during decoding.

Finally, due to the complex nature of reading, it is likely that genes involved in regulating cognitive processes such as memory, executive functioning, and attention may subsequently be related to reading and language. Two such "generalist genes" are *COMT*, which is involved in dopamine regulation in the prefrontal cortex (Meyer-Lindenberg et al., 2005), and *BDNF*, which regulates a variety of processes involved in brain development and plasticity (Numakawa et al., 2010). One recent study showed an association between the *COMT* $Val^{158}Met$ polymorphism (SNP rs4680) and neural activation in the reading circuit (e.g., the left occipito-temporal and superior temporal/middle temporal regions) during a word and pseudoword reading task, in addition to associations with phonological awareness and spelling (Landi et al., 2013). A second study showed that a common variation at *BDNF* SNP rs6265 (the BDNF $Val^{66}Met$ polymorphism) is associated with reading-related behaviors, including passage comprehension, and neural activation during reading in children (Jasińska et al., 2016). In light of these reading-related findings for genes associated with more general cognitive factors, it seems important that the field continue to consider the contribution of so-called generalist genes in examinations of the genetic basis of individual differences in reading and language.

6 | LIMITATIONS AND FUTURE DIRECTIONS

Although neuroimaging genetics provide a useful lens for investigating mechanisms that link genes to behavior in neurodevelopmental disorders, several important limitations must be addressed: reproducibility and convergence. Replication of genetic associations with language phenotypes has emerged as one key problem in the extant literature, both in genome-wide and targeted genetic association studies. Specifically, Carrion-Castillo et al. (2016) conducted a genetic association study of reading and language phenotypes with 17 of the most significant SNPs associated with these phenotypes in prior GWAS studies and failed to find any significant associations surviving correction for multiple comparisons in an independent sample from the Netherlands. Accordingly, neuroimaging genetics studies of reading and language should be interpreted with caution, especially because most do not include an independent replication cohort. Indeed, only one of the studies reviewed here included an independent replication cohort for neuroimaging-genetic analysis (Roeske et al., 2011). Furthermore, Grabitz et al. (2018) recently raised additional concerns with regard to genetics studies published in neuroimaging journals, namely, issues of sample size and power, calculation of effect size, correction for multiple comparisons, completeness of reporting, and complexity of analysis, in addition to the aforementioned replication problem. Indeed, very few of the studies reviewed here include reports of effect sizes, and several of those reported effect sizes for behavioral-genetic associations, but not imaging genetic associations, making it difficult to interpret the magnitude of reported effects.

Additionally, heterogeneity among study samples, measures, and methods likely contributes to a perceived lack of replication in some cases. The neuroimaging-genetic studies reviewed here include a great deal of variance in selection of samples, genetic markers, and analytic approaches that make it difficult to compare findings across studies. For example, Eicher et al. (2016) included a set of behaviorally associated SNPs on *DCDC2*, but not the *DCDC2* intron 2 deletion (*DCDC2d*) in their neuroimaging genetic analysis. This omission could lead to perceived lack of convergence with previous imaging genetic work on *DCDC2* by Meda et al. (2008) that found an association between gray matter volume and the *DCDC2d.* Likewise, differences in the acquisition and analysis of neuroimaging data such as examining white matter volume versus white matter microstructure (FA, RD, and AD) represent methodological heterogeneity that limits cross-study comparability. Large-scale studies

accounting for such variations are needed to confirm or reject the associations of specific SNPs with reading and language phenotypes. This poses a practical challenge that will require more collaborative cross-disciplinary efforts among researchers to collect the data required for replication. Transparent reporting of methods may also address issues of convergence such that future studies may provide appropriate comparison to existing findings.

7 | GENERAL CONCLUSION

The findings presented in this review illustrate the complex neurobiological underpinnings of reading and language disorders (See Table 2 for a summary of results from neuroimaging genetics studies reviewed in this paper). Though the application of neuroimaging genetic methods to research on SRD and DLD is in its early stages, common threads are emerging in the observed relations among gene, brain, and behavior. Indeed, imaging genetics research has linked variation on genes involved in aspects of neurodevelopment with brain structure and/or function in language-associated areas and reading/language performance. Although these links are not as clear for genes with less well-specified roles in neurodevelopmental processes or neuronal function, imaging genetics findings may guide new research that seeks to better understand the role of these genes in brain structure or function. Imaging genetics research also validates the involvement of a number of generalist genes, which contribute to individual differences in cognitive processing that affect reading and language performance. These contributions may explain additional genetic variance in reading and language performance beyond specific risk genes for dyslexia or DLD, thereby addressing the often-cited missing heritability problem.

The associations revealed between genes and neural activation suggest genetic sources of atypical neural functioning, but it remains unclear whether functional deficits arise due to anomalous brain structure and/or direct contributions of genes to neuronal excitation and metabolism. Limited by their correlational nature, neuroimaging genetic approaches cannot directly investigate causal mechanisms of SRD and DLD in humans, but these methods are key in building theoretical models of the etiologies of these prevalent neurodevelopmental disorders. Advances in neuroimaging technologies will help to fill some gaps in the mechanisms linking genes, brain, and behavior. One promising direction is the application of magnetic resonance spectroscopy (MRS) in neurogenetic research. This noninvasive tool allows for in vivo measurement of neurometabolites and neurotransmitters, thereby providing a neurochemical level of exploration for identification of connections between genes and neural function. This method affords human investigation of evidence linking genes and neurochemistry to atypical neural function in animal models such as the association between mutation of the *DCDC2* homolog in mice and altered neural activity driven by dysfunction of the neurotransmitter glutamate (Che, Girgenti, & LoTurco, 2014; Che, Truong, Fitch, & Loturco, 2016). Indeed, initial work utilizing MRS in humans has identified links between glutamate and choline and SRD and formed the basis for the application of the neural noise hypothesis to the study of SRD (Hancock, Pugh, & Hoeft, 2017; Pugh et al., 2014).

Further insight may arise from the combined use of neuroimaging and advanced DNA sequencing methods, including next-generation whole genome sequencing and whole exome sequencing, which afford the advantage of detecting small structural variants in addition to mutations and SNPs (Kornilov & Grigorenko, 2016). Ongoing developments in the use of next-generation sequencing along with advances in statistical approaches will support the discovery of new risk genes as well as complex gene by gene interactions and gene by environment interactions that further our understanding of the genetic bases of SRD and DLD.

Finally, the field will benefit from continued attempts at replication of extant findings as well as data sharing and combining that will allow for mega- and meta-analyses. The aforementioned lack of replication, lack of methodological overlap, and limited details in statistical reporting pose challenges to neuroimaging genetics research, but these issues may be ameliorated through the application of rigorous research and reporting methods. With these limitations in mind, neuroimaging genetic methods can make an important contribution by helping to constrain exploratory findings through identification of intermediate phenotypes that elucidate brain-based mechanisms linking genes to behavior in SRD and DLD.

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ENDNOTES

[1] For purposes of this review, specific reading disability is synonymous with reading disability (RD) and dyslexia, and developmental language disorder is synonymous with specific language impairment (SLI) and language impairment (LI).

[2] Allele frequency data are publicly available in the dbSNP database: https://www.ncbi.nlm.nih.gov/snp (Sherry et al., 2001).

[3] Unique identifiers called reference SNP (rs) ID numbers are assigned by The National Center for Biotechnology Information (NCBI) for consistent identification and comparison of polymorphisms across individuals (Kitts, Phan, Ward, & Holmes, 2013).

[4] Although negative findings have also been reported (Paracchini et al., 2011; Scerri et al., 2017).

[5] PING is a multi-site study and corresponding database that includes standardized behavioral measures, imaging phenotypes, and whole genome genotyping (Jernigan et al., 2016).

[6] The non-dominant allele (A) identified for this study according to the Japanese Hapmap ratio does not correspond to the rs7794745 risk-allele (T) identified in the Whalley et al. (2011) study described above.

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APPENDIX

GLOSSARY

Allele: One of several alternative forms of a unit (base) of DNA that may be present at a given location on a chromosome

Axon guidance: The neurodevelopmental signaling process by which neuronal projections (axons) extend toward a target

Bioinformatics analysis: The application of computational methods to the study of genetic data

GWAS (Genome-wide association study): An exploratory approach to identify genetic markers of traits and diseases by searching across the genome for locations in which the frequency of a polymorphism is associated with a trait of interest

Haplotype: A combination of genetic variants that are inherited together

Heterozygote/heterozygous: An individual's homologous chromosomes express different genetic variants at a given location

Homozygote/homozygous: Both of an individual's homologous chromosomes express the same genetic variant at a given location

Insertion–deletion polymorphisms (indels): A genetic variation in which one or more units of DNA are added (insertion) or removed (deletion)

Intergenic region: A portion of a chromosome that lies in between genes; these stretches of DNA do not code for proteins and are often of unknown function, though some may have regulatory effects on nearby genes

Intron: A portion of the DNA sequence within a gene that does not code for proteins

Linkage analysis: A method used to identify links between genetic markers (a DNA sequence in a chromosome) and traits or diseases by examining patterns of inheritance among individuals within a family who exhibit the trait of interest. Genetic markers that are specifically carried by family members who exhibit the given trait are inferred to be related to that trait and may be targeted as links to the trait in the general population.

Polymorphism: A varying form of a small structural unit of the DNA molecule (a base or series of bases) which can be expressed in different forms or numbers of repetitions

Sequencing: The process of identifying the order of the small units (bases) that make up DNA and genes

SNP (single nucleotide polymorphism): A genetic variation in which one unit of the DNA molecule (one base) is expressed in an alternative form (e.g., G or Guanine instead of A or Adenine)