Imaging-Genetics in Dyslexia: Connecting risk genetic variants to brain neuroimaging and ultimately to reading impairments

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Abstract

Dyslexia is a common pediatric disorder that affects 5-17% of schoolchildren in the United States. It is marked by unexpected difficulties in fluent reading despite adequate intelligence, opportunity, and instruction. Classically, neuropsychologists have studied dyslexia using a variety of neurocognitive batteries to gain insight into the specific deficits and impairments in affected children. Since dyslexia is a complex genetic trait with high heritability, analyses conditioned on performance on these neurocognitive batteries have been used to try to identify associated genes. This has led to some successes in identifying contributing genes, although much of the heritability remains unexplained. Additionally, the lack of relevant human brain tissue for analysis and the challenges of modeling a uniquely human trait in animals are barriers to advancing our knowledge of the underlying pathophysiology. *In vivo* imaging technologies, however, present new opportunities to examine dyslexia and reading skills in a clearly relevant context in human subjects. Recent investigations have started to integrate these imaging data with genetic data in attempts to gain a more complete and complex understanding of reading processes. In addition to bridging the gap from genetic risk variant to a discernible neuroimaging phenotype and ultimately to the clinical impairments in reading performance, the use of neuroimaging phenotypes will reveal novel risk genes and variants. In this article, we briefly discuss the genetic and imaging investigations and take an in-depth look at the recent imaging-genetics investigations of dyslexia.

Keywords

Dyslexia; neuroimaging; genetics; imaging-genetics

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Conflict of Interest

The authors declare competing financial interests: Yale University has applied for a patent covering the complex tandem repeat and deletion in READ1 (inventor: J.R.G.), and sublicensed it to JS Genetics, Inc. J.R.G. is a founder and equity holder of JS Genetics, Inc.

1. Introduction

1.1 Background of Dyslexia

Language based learning disabilities are the most common learning disabilities in schoolchildren in the United States [1]. Dyslexia, also known as reading disability, comprises a majority of these language based learning disabilities. Prevalence estimates vary depending on diagnostic criteria, with estimates ranging from 5-17% in western countries including the United States and the United Kingdom [2]. Nonetheless, dyslexia is common in pediatric populations across the globe and remains a lifelong impairment. These unexplained difficulties in reading can negatively impact a child's academic performance, reduce self-perception of cognitive abilities, and yield various undesirable socioeconomic consequences [2-3]. Neuropsychologists have investigated the specific reading and language processes that underlie dyslexia. Phonological processing is widely viewed as the core deficit in dyslexia, although deficits in reading comprehension, orthography, auditory stimuli integration, and semantic processing are also often observed [2, 4-9].

Interventions are available to remediate these reading deficits and help in the development of proficient reading and academic skills. Interventions are most successful when they are applied at younger ages, making early diagnosis a priority for optimal outcomes [9-10]. Currently, to make a diagnosis, trained neuropsychologists and educational professionals perform an exhaustive series of expensive neurocognitive assessments on each child. This, however, requires that the child has started to develop reading and language skills, which can delay early detection. Additionally, the expenses of diagnostic neurocognitive testing and need for trained professionals are significant roadblocks to the delivery of effective treatment to affected children. The challenges of early detection of a behavioral disorder make testing for genetic factors, detectable biomarkers, and/or neuroimaging signatures attractive alternatives.

1.2. Genetic Etiologies of Dyslexia

Family studies have long shown that dyslexia and overall reading abilities have significant genetic components, with heritability estimated at 54-84% [11-12]. Over the past two decades, genetic studies have examined which loci and specific genes contribute to dyslexia and reading skills. As with most complex and neurobehavioral traits, these investigations have produced both successes and failures. Genetic linkage studies have identified nine dyslexia genetic loci termed DYX1-DYX9 spanning 1-20 million bases on 8 different chromosomes, each with varying degrees of evidence supporting their role (Table 1). Within these loci, several dyslexia risk genes have been identified including *DCDC2, KIAA0319, TTRAP*, and *THEM2* on chromosome 6 [13-15], *DYX1C1* and *CYP19A1* on chromosome 15 [16-18], *C2orf3* and *MRPL19* on chromosome 2 [19-20], *ROBO1* on chromosome 3 [21-22], and *KIAA0319L* on chromosome 1 [23]. Outside of these DYX loci, other genes are also associated with dyslexia and performance on reading tasks, including *FOXP2* and *CNTNAP2* on chromosome 7 as well as *ATP2C2* and *CMIP* on chromosome 16 [24-29]. Of these, the most replicated and well-studied are *DCDC2* and *KIAA0319* on chromosome 6, *DYX1C1* on chromosome 15, and *FOXP2* and *CNTNAP2* on chromosome 7. In-depth reviews discussing the genetics of dyslexia and related language disorders have been published elsewhere [30-34].

To define phenotypes in genetic studies of dyslexia and reading processes, investigators have primarily used neurobehavioral phenotypes, similar to those used to diagnose children in schools and clinics. There are advantages to using a solely behavioral approach in defining phenotypes. First, neurobehavioral reading measures match the clinical presentation of cases in schools and the tests used to diagnose affected individuals. Thus, genetic variants

that show association with these phenotypes are likely to be relevant to the clinical neurobehavioral outcome of interest. Second, the neurobehavioral batteries used to define dyslexia are normalized, validated measures that have been used in research and clinically for decades. This allows for reliability and accuracy in ascertaining reading abilities and allows for results to be compared across disciplines and investigations. Third, researchers have developed these neurobehavioral batteries to examine several components of reading and language, such as phonological awareness and semantic processing, to ascertain the effects of various factors on different disorder subtypes and sub-processes. These specific batteries can examine the effects of genetic factors on specific reading and language processes.

However, when looking specifically at genetic and biological investigations of dyslexia, the use of neurobehavioral reading tests can have disadvantages. There are numerous intermediary factors that separate genes from the downstream reading processes. Genetic factors can lead to changes in gene expression, protein expression, protein folding, and protein signaling, along with many other functional changes. Additionally, recent studies have demonstrated the importance of non-coding elements including miRNAs and other non-coding RNAs which can influence gene and protein expression as well protein structure itself. These changes in gene and protein function have direct effects on protein-protein, protein-DNA, protein-RNA, and other protein-species interactions. These changed interactions then have a larger effect on cellular and tissue functionality. It is then changes in these functionalities that can give rise to reading impairments and the ultimate observed neurobehavioral phenotype (Figure 1). Using only neurobehavioral measures to characterize dyslexia and reading processes can overlook the mechanistic implications of risk genes and variants, and ultimately the ascertainment of the molecular mechanisms, pathways, and gene networks.

With these limitations in mind, researchers have begun to look to other means to bridge the gap between gene, mechanism, and clinical presentation. One common method is to use animal models to functionally interrogate genes identified by human studies. These include knockdown, knockout, and knock-in genetic models in systems including *Drosophila*, mouse, rat, *C. elegans*, among numerous others. These systems allow for the *in vivo* examination of gene and protein function to characterize molecular and functional mechanisms underlying disease. Unfortunately, modeling human-specific genetic elements and human-specific phenotypes in animal models can prove difficult, especially for non-essential traits such as reading and language that have not evolved in many species and do not influence overall reproductive fitness. Although much can be and has been learned about specific gene function by modeling these human-specific non-essential phenotypes in animal models, there remains a need for a means to examine these processes *in vivo* that is directly related to reading and language abilities.

1.3. Use of Imaging in Dyslexia

One strategy researchers have begun to explore is *in vivo* neuroimaging techniques to gain structural, connectivity, and functional insights into the reading and language centers of the brain (Table 2). These studies have detected neuroimaging differences between subjects with dyslexia and non-impaired controls. Subjects with dyslexia have structural differences compared to non-impaired controls, both in grey matter density and in white matter microstructure connectivity and integrity [35-47]. Functional magnetic resonance imaging (fMRI) studies show that subjects with dyslexia display different patterns of brain activation during reading tasks compared to non-impaired controls [48-56]. Generally, impaired subjects show increased bilateral, symmetric brain activation patterns as opposed to the left-stereotyped activation patterns in non-impaired individuals [57]. Detailed reviews of dyslexia imaging studies are published elsewhere [58].

Although studies have shown various neuroimaging differences between subjects with and without dyslexia, imaging techniques are currently not sensitive or reliable enough to be used as a diagnostic tool in the clinic. However, in research, the prospect of integrating these neuroimaging data with genetic and neurobehavioral data to gain a mechanistic model of gene, brain function and structure, and ultimate behavioral phenotype is attractive, although difficult and complex. Determining whether these neuroimaging differences cause reading deficits or are a result of having dyslexia can be difficult. The use of various data modalities including human genetic, neuroimaging, and animal model studies can help untangle these complex relationships. The remainder of this review aims to discuss the investigations that have attempted to integrate neuroimaging data with genetic and neurobehavioral data (termed imaging-genetics), followed by comments on the promise and future of imaging-genetics in examining dyslexia. To date, imaging-genetic studies of dyslexia have focused on the following genes: (1) *DCDC2*, (2) *KIAA0319*, (3) *FOXP2*, (4) *CNTNAP2*, and (5) *DYX1C1/C2orf3/MRPL19* (Table 3).

2. Imaging-Genetics Studies of Dyslexia

2.1. The DYX2 Locus: *DCDC2* and *KIAA0319*

The DYX2 locus is located on chromosome 6p22 in which two dyslexia risk genes, *DCDC2* and *KIAA0319*, are encoded (Table 1). *DCDC2* and *KIAA0319* are the two most replicated dyslexia risk genes, having been associated with dyslexia and overall reading skills in numerous studies [13-15, 29, 59-73]. Animal models of the effects of mutations in these genes have been examined in mice, rats, and *C. elegans*. *KIAA0319* and *DCDC2* knockout mice have shown several behavioral impairments including spatial memory and response to acoustic stimuli, but again underscore the difficulties in modeling a uniquely human trait in non-human systems [74]. *In utero* RNAi knockdowns of *DCDC2* and *KIAA0319* in embryonic rats exhibited aberrant neuronal migration, suggesting that dyslexia may result in dysfunction in neuronal migration during fetal development [13, 75-77]. *In utero* RNAi Kiaa0319 knockdowns in rats have also shown the influence of this gene on dendrite morphology, migratory defects resulting in heterotopias in white matter, and changes in corpus collosum area along with deficits in responses to acoustic stimuli and impaired spatial learning [76, 78-79]. Preliminary work in *C. elegans* showed that *DCDC2* affects ciliated neurons, suggesting specific neuron types that may be affected by risk variants [80]. Therefore, the functional implications on neuronal migration and other neural phenotypes suggest that *DCDC2* and *KIAA0319* have distinct neuroimaging impacts. These neuroimaging implications of *DCDC2* and *KIAA0319* may mediate their effects on reading performance. To this end, recent investigations have examined *DCDC2* and *KIAA0319* using various neuroimaging techniques.

Imaging-genetic studies have started to examine the contributions of *DCDC2* to neuroimaging phenotypes using structural and functional MRI data. Our group found a relationship between grey matter volume in subjects with dyslexia and a microdeletion located within intron 2 of *DCDC2* [81]. This microdeletion contains a functional variant, termed READ1, which is a highly polymorphic complex tandem repeat with over 30 observed alleles [13, 73, 82]. The READ1 element has been associated with dyslexia in numerous independent cohorts [13, 73, 83-84]. The READ1 element has the capability to modulate *DCDC2* expression *in vitro* and specifically binds the transcription factor ETV6 [73, 82]. Meda et al. showed that this variant has downstream effects upon grey matter volume in dyslexic subjects, possibly mediated by its effect on *DCDC2* and/or other gene expression [81]. Further, Jamadar et al. demonstrated an association between SNPs within *DCDC2* and grey matter volumes in the superior prefrontal, temporal, and occipital networks in subjects with schizophrenia, defined using parallel independent component analysis (ICA) [85]. Darki et al. recently reported association of *DCDC2* SNPs with white

matter volume in the left temporo-parietal region [86]. The authors then connected white matter volume to reading skills in the same subjects, suggesting that *DCDC2* influences white matter volume which then influences reading performance. This investigation attempts to connect the dots from genetic variants, to neuroimaging phenotype, to the ultimate neurobehavioral clinical presentation. These studies indicate that grey and white matter volumes are influenced by *DCDC2*, possibly by changes in gene expression that influence neuronal migration, and then exert an effect upon reading performance. Regionally, volumetric differences in the temporo-parietal, superior prefrontal, temporal, and occipital areas appear to be influenced by the DYX2 locus.

READ1 in *DCDC2* was further characterized in Cope et al. 2012 using fMRI during four reading-related tasks [87]. Alleles 4 and 8 of READ1 were associated with brain activation patterns in the left anterior inferior parietal lobe and right lateral occipital temporal gyrus during semantic processing tasks. These associations were hypothesized to be protective in nature as their direction of effect was similar to brain activation patterns of non-impaired individuals. The READ1 element appears to have mediatory effects on gene expression and neuroimaging phenotypes that then influence reading performance. Using resting state fMRI data, Jamadar et al. also showed association of *DCDC2* variants with a Broca-medial parietal network in both schizophrenic and non-impaired cohorts [88]. In addition to grey/ white matter volume, *DCDC2* appears to alter brain activation patterns and regional connections in various anatomic language and reading centers.

Similar to *DCDC2*, *KIAA0319* associated with differences in grey matter volumes in the Darki et al. and Jamadar et al. studies, once again tying the DYX2 locus to volumetric differences in white/grey matter volume [85-86]. Examining grey matter volumes using voxel-based morphometry, Jamadar et al. found superior and inferior cerebellar networks were related to *KIAA0319* [85]. Darki et al. also reported association of *KIAA0319* with white matter volume in the left temporo-parietal region [86]. These structural studies depict a connection from *KIAA0319* to white/grey matter volumes, which then appear to influence reading skills.

Using fMRI data, Pinel et al. observed an association between a variant in *THEM2* and lower asymmetric activation of the posterior superior temporal sulcus during reading and phonology tasks [89]. The observed lower asymmetry of brain activation patterns by genetic marker is similar to the observed asymmetry in affected individuals. Although the associated marker in the Pinel et al. study was located within *THEM2*, it appears that this marker captures variation from the *KIAA0319* risk haplotype. This risk haplotype has been associated with dyslexia numerous times and encompasses the 5' portion of *KIAA0319*, along with neighboring genes *TTRAP* and *THEM2* [64, 66, 70, 72, 77, 90]. This *KIAA0319* risk-haplotype has been associated with lower *KIAA0319* gene expression [91]. In fact, the *DCDC2* READ1 element and *KIAA0319* risk haplotype have been shown to interact genetically in a synergistic manner [66, 73, 91]. However, whether these genomic loci interact physically remains to be determined, although the possibility of an interaction between a regulatory element and a promoter region is intriguing. Using resting state fMRI in schizophrenia and non-impaired groups, Jamadar et al. found a left Broca-superior/ inferior parietal network was related to two *KIAA0319* SNPs in non-impaired individuals. In both schizophrenic and non-impaired individuals, a left Wernicke-fronto-occipital network was related to two *KIAA0319* SNPs [88]. A bilateral Wernicke-fronto-parietal network was related to one *KIAA0319* SNP only in non-impaired individuals. These differences between schizophrenia and non-impaired groups indicate that non-impaired individuals may utilize different parts of the brain during reading tasks than those with a distinct neurobehavioral or neuropsychiatric disorder. Nonetheless, *KIAA0319* contributes

to a variety of imaging phenotypes particularly in terms of grey/white matter volumes, brain circuitry, and brain activation patterns during reading-related tasks.

2.2. *FOXP2*

FOXP2 and *CNTNAP2* both reside on chromosome 7 and were implicated in other disorders before being examined in dyslexia. *FOXP2* was first implicated in a family segregating a severe form of dyspraxia of speech, designated the KE family [26, 93-96]. Following this discovery, *FOXP2* has become the most widely studied gene related to language, including a myriad of approaches from animal models such as mice and finches to *in vitro* molecular work to examine its regulatory capabilities [97-102]. In fact, many have examined the human specific nature of *FOXP2* expression and function and correlated this with the evolution of language in humans [103-107]. *FOXP2* is a regulator of neurogenesis during embryonic development [108]. Mouse models have been generated carrying mutant Foxp2. These animals exhibit abnormal ultrasonic vocalizations, thought to be a phenotype to model human speech development, as well as other disorders including developmental delay, motor function, and brain development [108-111]. Expression of human, but not mouse, *FOXP2* enhanced progenitor and neuron development [111-112]. However, how the expression and function of *FOXP2* influences the brain and language skills mechanistically still remains to be elucidated.

The first imaging investigations of *FOXP2* were of structural differences among affected and unaffected members of the KE family. Although speech impairments and speech dyspraxia are distinct disorders from dyslexia, the neuroimaging implication for a Mendelian disorder of a single gene (in this case *FOXP2*) can make a significant contribution to the pathobiology of the *FOXP2* gene and where/how this gene functions. As this family is affected with a single gene disorder, the use of related individuals can aid to remove other genetic and environmental factors that may have influenced neuroimaging measures. Multiple imaging studies of this family have found structural abnormalities, particularly in grey matter density [113-115]. These include decreased grey matter density bilaterally in the caudate nucleus, cerebellum, and inferior frontal, and increased grey matter density bilaterally in the planum temporal gyrus [113-115]. These changes in neuroimaging measures, particularly in grey matter density, appear to be a consequence of the *FOXP2* mutation and consequently, could influence language in these affected family members.

Investigators have also performed fMRI studies of KE family members [116]. Non-impaired family members who did not have the causal *FOXP2* variant exhibited normal left dominant patterning of brain activation during reading tasks. Affected individuals with the mutant *FOXP2* exhibited different brain activation patterns with increased posterior and bilateral brain activation. These affected family members also exhibited reduced activation of Broca's area, as well as other cortical language related regions and the putamen. A PET functional imaging study showed underactivation of the left supplemental motor area (SMA), left subjacent cingulate cortex, and left preSMA/cingulate cortex and overactivation of the left caudate nucleus and left ventral prefrontal region in affected family members [115]. These studies of this one family demonstrate the utility of and amount of insight gained from examining rare variants with large effect. Beyond the KE family, new studies have examined the role of *FOXP2* in reading. Recent studies by Wilcke et al. in subjects with dyslexia and Pinel et al. in non-impaired individuals found differences among variants in *FOXP2* in regional brain activation during reading tasks including temporo-parietal, inferior frontal, and precentral brain regions [25, 89]. Together, these studies of rare and more common variants within *FOXP2* show the important role it plays in overall language and reading skills throughout the brain.

2.3. *CNTNAP2*

FOXP2 is a transcription factor and modulates DNA transcription at numerous loci throughout the genome, underscoring the importance of transcriptional regulation in dyslexia and other neurobehavioral disorders. Interestingly, one of its gene targets is the cell adhesion gene *CNTNAP2*. *CNTNAP2* has been linked and associated with numerous neurobehavioral and neuropsychiatric disorders including Tourette's syndrome, schizophrenia, speech delay, and autism spectrum disorders [117-124]. Recently, the associations of *CNTNAP2* were expanded to included language impairment and dyslexia [24, 29, 125]. *CNTNAP2* is expressed in the frontal and temporal lobes of developing brain and in frontal cortex of adults [126]. These areas are vital to reading and language development. *CNTNAP2* encodes the Caspr2 protein, which functions in voltage gated channels at Nodes of Ranvier and is important in cellular migration [127-129]. This function suggests that variants in *CNTNAP2* may cause abnormalities in the propagation of action potentials throughout neural circuits and integration of written language stimuli. It has also been hypothesized that *CNTNAP2* helps to mediate interactions between neurons and glia [130]. Connecting *CNTNAP2* molecular neural functions to the observed language associations by imaging-genetics would help explain how changes in *CNTNAP2* may cause impairments in reading and language.

As *CNTNAP2* encodes a protein that functions in cellular migration, Tan et al. used structural MRI to examine grey and white matter volume implications of a previously associated variant, rs7794745 [131]. Most samples in imaging-genetic studies are small in size; however, this study examined MRI measures in over 300 children. This larger sample size, in addition to increasing statistical power, also allowed the investigators to compare subjects homozygous for the risk allele with subjects homozygous for the nonrisk allele. There were differences in gray and white matter volumes in regions of interest between these two groups. Specifically, they observed reduced grey matter in fusiform, posterior cerebellar hemispheres, posterior occipital cortices, cerebellar vermis, left superior cerebellum, and right frontal pole. There were reductions in white matter volume in posterior thalamic radiation (thalamus to posterior parietal/occipital cortex), right caudal inferior fronto-occipital fasciculus (frontal/occipital lobe, fusiform), and right rostral cingulum. To expand on their findings with grey/white matter, Tan et al. used DTI to examine the fractional anisotropy (FA) implications of the rs7794745 variant [131]. There were sex-specific reductions in FA, specifically in the right rostral inferior fronto-occipital fasciculus in males and the right anterior thalamic radiation/putaminal head in females. These sex-specific differences in white matter tracts may contribute to gender differences of dyslexia and language disorders.

In addition to *CNTNAP2*s effects on brain structure and circuitry, other studies have examined the effects of *CNTNAP2* risk variants on brain activation patterns. Scott-Van Zeeland et al. 2010 examined frontal lobar connectivity and the *CNTNAP2* variant rs2710102 using fMRI [132]. There was reduced activity in medial prefrontal cortex, along with more widespread and bilateral connectivity in frontal cortex and anterior temporal pole in risk subjects. Subjects with the non-risk variant had a stereotypical left-lateralized network, including the left inferior frontal gyrus, insula, anterior temporal pole, superior temporal gyrus and angular gyrus, usually seen in non-impaired subjects. These associations were replicated in two additional small samples, including the right middle frontal gyrus and left interacalcarine cortex. These replication cohorts also displayed the same network of activation patterns. Whalley et al. examined the rs7794745 and rs2710102 risk variants of *CNTNAP2* and fMRI brain activation patterns [133]. They found that healthy individuals with the risk allele had a significant increase in activation of right inferior frontal gyrus [analogous to Broca's area] and right lateral temporal cortex, similar to increased right (i.e. bilateral) brain activation in risk allele groups in other studies. These studies implicated

CNTNAP2 as altering brain activation patterns in a similar fashion to those seen in subjects with dyslexia. With its associations with multiple disorders, however, it remains to be seen whether these changes in brain activation specifically contribute to dyslexia or contribute to core deficits observed in multiple neurobehavioral disorders.

2.4. Other Genes: *DYX1C1* and *MRPL19/C2orf3*

There have been limited imaging-genetics studies of other dyslexia loci and genes, namely *DYX1C1* on chromosome 15 and the DYX3 locus on chromosome 2. *DYX1C1* on chromosome 15q21 was first identified in a family with dyslexia co-segregating with a translocation disrupting the *DYX1C1* gene [16]. Efforts at replicating the association of this gene have been mixed, but positive replication has been achieved in several cohorts [17, 134-138]. Most *in vivo* work with *DYX1C1* has occurred using *in utero* RNAi knockdown models in rats, similar to those completed with *KIAA0319* and *DCDC2* [71, 139-143]. Behaviorally, these animals display impairments in analogous domains including working memory, auditory processing, and spatial reasoning [144]. Anatomically, there are neuronal migratory and laminar disruptions, and a subset of the rats display hippocampal heterotopias [145-146]. Pathway analyses have bolstered these neurological implications by linking *DYX1C1* with other major genes involved in neuronal migration and brain development pathways, along with cytoskeletal proteins similar to *DCDC2* and *KIAA0319* [147-148]. *DYX1C1* has also been linked to ciliated neurons and cilary function in migration [148-149]. Investigators have found associations of *DYX1C1* with grey and white matter volumes in a superior cerebral network and temporo-parietal regions, respectively [85-86]. The role of *DYX1C1* in neuronal migration may have an impact on the development of grey and white matter.

The DYX3 locus on chromosome 2 is less studied than the other genes presented in this review, but is centered on *MRPL19* and *C2orf3* with mixed results in replication analyses [19, 150-153]. SNPs in these genes have shown association with reading and language performance in multiple cohorts, including a study by Scerri et al [20]. Scerri et al also found an association of variants in DYX3 and white matter structure in the posterior of the corpus callosum and cingulum, regions that connect large portions of the cortex in the parietal, occipital, and temporal lobes [20]. Although not yet as widely studied, these studies offer a promising start into understanding the implications of *DYX1C1* and the DYX3 locus on brain imaging phenotypes.

3. Where Imaging-Genetics of Dyslexia Currently Stands

3.1 By Neuroimaging Method

Neuroimaging technology can provide a wide array of data, including those on structural volume, grey/white matter volume, resting state, brain activation during specific reading-related tasks, connectivity, DTI, and FA. They may be inherently interrelated, but each reveals a nuanced, unique aspect of brain functionality. Therefore, a gene's association with these various imaging measures can reveal nuanced, specific as well as universal, widespread roles of these genes in brain development and function.

So far, there have been a variety of associations between the specific genes presented in this review and neuroimaging measures. All studied genes in this review (*DCDC2, KIAA0319, FOXP2,* and *CNTNAP2, DYX1C1,* and *C2orf3/MRPL19*) associated with grey and white matter volumes. These studies suggest that the genes that impart risk to dyslexia fundamentally influence and alter brain development. Changes in grey and white matter volume as well as overall structure may influence the proper propagation and/or integration of language stimuli throughout critical brain regions of interest, yielding the behavioral deficits in phonology, semantics, spelling, and overall reading comprehension. These

genetic associations with grey and white matter volume differences lend credence to the current neuronal migration hypothesis underlying dyslexia. Animal models of *DCDC2, KIAA0319*, and *DYX1C1* all exhibit abnormalities in the migration of neurons from the ventricular zone into the cortex. These abnormalities in neuronal migration in animal models may mirror the differences in grey and white matter volumes observed in imaging-genetics studies in humans. These changes in volumes may bring about a yet unidentified effect, perhaps alterations in brain activation patterns and/or efficient integration and propagation of action potentials that influence reading skills.

The four more widely studied genes (*DCDC2, KIAA0319, FOXP2*, and *CNTNAP2*) presented in this review have shown association with fMRI brain activation patterns during reading-related tasks. These changes in brain activation patterns suggest that risk variants contribute to the ability of specific regions of the brain to fluently process and respond to written language stimuli. Resting state fMRI identified networks connecting neural language centers where *DCDC2* and/or *KIAA0319* risk variants may also contribute to deficits in reading and language fluency. Changes in both brain activation patterns and networks may be a consequence of aberrant neuronal migration that results from altered gene expression as modeled in experimental animals. Failure of neurons and supporting cells to migrate to proper locations may alter the brains ability to efficiently integrate language stimuli and propagate the appropriate neural response in specific critical brain regions for fluent language. Other imaging technology including PET and FA has been less widely studied. However, *FOXP2* variants have been shown to associate with differences in activation during PET, which supplements and bolsters functional studies using fMRI. *CNTNAP2* showed associations with FA, again showing that *CNTNAP2* influences brain circuitry important in reading and language. Imaging-genetic studies have shown that risk genes identified using neurobehavioral phenotypes have implications for brain structure, grey/white matter, brain connectivity and circuitry, and brain activation during reading-related tasks that influence reading and language performance and deficits.

3.2 By Brain Region

As imaging-genetic studies of dyslexia increase in number, how and where dyslexia risk genes function will become more apparent. In addition to brain gene expression data recently available, imaging data can aid in identifying where risk genes normally function, where gene dysfunction can lead to disorders, and possible signatures of the disorder state. There also may be gene-specific, location-specific dysfunctions that are related to dyslexia and other higher-order cognitive disorders. By integrating behavioral, genetic, and imaging data, we can identify brain regions with gene-specific effects (i.e. only a small subset of risk genes function in this region) or with universal effects (i.e. all/many risk gene function in this region). For example, *DCDC2, KIAA0319, FOXP2*, and *CNTNAP2* have all shown associations in Broca's area and the inferior frontal gyrus (Figure 2a). Broca's area and inferior frontal gyrus are main language centers in the brain, so it is logical for many dyslexia risk genes to be associated with various imaging measures in these areas. Similarly, increased right brain activation during reading-related tasks was observed in risk allele variants of *KIAA0319, FOXP2*, and *CNTNAP2*, as opposed to the typical left-side dominant brain activation seen in non-impaired and non-risk groups. However, with *KIAA0319*, this loss of asymmetry was seen only in the posterior superior temporal sulcus (Figure 2b). More widespread, bilateral brain activation patterns were seen in *FOXP2* and *CNTNAP2* risk variants, which may explain why *FOXP2* and *CNTNAP2* are associated with a litany of neurological disorders and *KIAA0319* is somewhat specific to reading, language, and cognition. *FOXP2* was the only gene linked with the caudate nucleus and showed associations with grey matter and PET scan overactivation (Figure 2c). *DCDC2, KIAA0319*, and *DYX1C1* (white matter) along with *FOXP2* (fMRI activation) associated with the

temporo-parietal regions of the brain (Figure 2a). The associations with Broca's area/inferior frontal gyrus as well as the temporal-parietal regions suggests that connections between these areas, possibly including the inferior fronto-occipito fasiculus which showed a relationship with *CNTNAP2*, will be important areas for imaging-genetics research in the future (Figure 2d). However, lack of association does not necessarily mean that these genes do not function or relate to these regions or neuroimaging data of interest. Imaging-genetic studies of dyslexia are still limited in number and many hypotheses remain to be tested with sufficient statistical and biological power.

3.3 Current Limitations of Imaging Genetics

As with every emerging field and technology, there are various limitations of the initial imaging-genetics studies of dyslexia. (1) The first limitation in most imaging-genetics studies is the relatively small sample size. Small sample size in genetics studies can be especially worrisome due to population stratification and lower minor allele frequencies, which can also lower statistical power. The largest imaging study reported to date is that of Tan et al., which included approximately 300 subjects [131].. Although imaging-genetic studies can be daunting in terms of expense, time, and the amount of data to interpret, larger studies following the models of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www.loni.ucla.edu/ADNI/) and Pediatric Imaging Neurocognition Genetics study (PING) (http://ping.chd.ucsd.edu/) are necessary to expand the promise of imaging-genetic studies. New study designs including longitudinal imaging-genetics investigations on both impaired and non-impaired individuals could provide a means to temporally dissect the genetic contributions to brain and neurocognitive development. (2) Another difficulty is that subjects are from a relatively healthy pediatric population. Recruitment of these individuals can be difficult since there is little to no incentive to participate. (3) Interpreting what imaging data and associations with genetic and behavioral factors actually mean in a biological context is challenging. Although there are numerous hypotheses regarding the actual meaning of increased brain activation in fMRI, brain circuitry revealed through resting state fMRI and FA studies, and connectivity measures through DTI, it is still difficult to make definitive conclusions about the biological and behavioral implications of these data. Discerning whether these neuroimaging phenotypes are causal of or resulting from case status is challenging due to the inherent complexity and plasticity of the brain. Further neurophysiological and molecular interrogation using cell-based and organism models as well as longitudinal imaging-genetic studies can help in determining causal and temporal relationships. Adding to the inherent difficulty of these studies are the nuanced nature of neuroimaging, and the currently underdeveloped methods and standards for reporting findings to other scientists and the lay public. (4) All of the presented studies started with a small subset of genetic variants and then examined the implications of these specific genetic factors on brain imaging measures. Selection bias along with ignoring most of the genome could lead to misleading and incomplete results and hypotheses. (5) With the exception of Darki et al., most of the presented imaging-genetic studies of dyslexia examine the effects of genetic variants on behavior and brain imaging data independently, instead of fully integrating them together (Figure 3). Such an analytical strategy does not take advantage of the vast amount of data collected on single subjects. Integration of these data could be powerful in unraveling the mystery and for developing risk models of neurobehavioral disorders such as dyslexia.

4. The Future of Imaging-Genetics in Dyslexia

Currently, we have an incomplete view of the biological etiologies underlying dyslexia. Neuropsychological, genetic, molecular, and imaging studies have made much progress into identifying impairments, candidate genes/signatures, and possible pathways that may contribute to the deficits observed in dyslexia and related disorders. However, how these

varying levels of phenotype interact and relate to each other to lead to the ultimate phenotype remains elusive. Additionally, currently, only neurobehavioral batteries are used as a diagnostic tool for dyslexia. Imaging and genetic tools are currently unable to specifically and sensitively identify children with and without dyslexia. Future studies are needed to identify and to develop risk models to accurately use imaging and genetic data as a diagnostic or screening tool. Currently, imaging-genetics studies are used to gain a more mechanistic understanding into the pathophysiology of dyslexia and reading-related processes.

The studies presented in this review represent some of the first attempts to integrate genetic, molecular, imaging, and neurobehavioral data to characterize dyslexia. These studies attempt to connect the dots from genes, to molecular and cellular function, to changes at the neurological and brain level, and finally to the ultimate neurobehavioral clinical presentation of impaired reading (Figure 1, Figure 3). Imaging-genetics provides an ethical means to gain mechanistic insight into the pathophysiology in human subjects *in vivo*. Instead of relying upon animal models that may approximate the behavioral and biological deficits seen in dyslexia, human imaging-genetics allow for the direct examination of human risk genetic variants with imaging data directly related to reading and language processes. This could represent the beginnings of a logical progression of risk factors to neuroimaging signatures to neurobehavioral presentation that may allow for earlier detection and remediation of affected individuals. Early detection in dyslexia is vital for optimal remediation and academic outcomes.

The advent of cheaper, more advanced imaging and genetic technologies has made the integration of human brain imaging and genetics to investigate dyslexia possible. Imaging-genetics remains an immature field, but the studies presented in this review have begun the promising use of imaging and genetics to gain *in vivo* insights. So far, imaging-genetic studies of dyslexia have relied on the positive results from neurobehavioral genetic studies to identify candidate genes and variants, which are then used to analyze independent imaging data. Although producing interesting results, hypothesis driven studies informed by past neurobehavioral studies limit the extent to which pathophysiology can be explored. These studies can only reveal possible implications of these very specific genetic variants on brain imaging phenotypes. They cannot reveal other genetic contributors to the overall neurobehavioral reading deficits nor the imaging phenotype changes associated with dyslexia. Hypothesis-free genetic studies, similar to those seen commonly in human genetics such as genome-wide association studies (GWAS) and sequencing studies, could reveal new genes and pathways that contribute to alterations in brain imaging phenotypes, and how they contribute to the ultimate neurobehavioral phenotypes. In addition, new imaging technologies, such as Nuclear Magnetic Resonance (NRM) and Single Photon Emission Computed Tomography (SPECT), can detect metabolites and neurotransmitters *in vivo*. Recent genetic and neurobehavioral analyses have begun to implicate neurotransmitter signaling in language disorders [154-155]. Therefore, directly examining these signaling molecules and other metabolites in the brain could lead to further characterization of mechanisms underlying reading and language impairments.

A major hurdle underlying imaging-genetics as a field is the analyses of such large and diverse datasets. Typical GWAS datasets contain over 1 million markers and can be increased drastically with the imputation of non-genotyped SNPs. Sequencing data contain even larger amounts of data. Imaging data can comprise thousands of data points depending on which level analysis is performed (voxel-based, regions of interest, various circuits and networks). Examining each of these data points in a hypothesis-free manner would result in an extraordinary number of tests, which would require an exorbitant correction for multiple testing. Integrating these together in addition to neurobehavioral phenotypes can result in

millions of hypotheses and an inordinate amount of computation costs and data to analyze. Data reduction methods, such as parallel ICA performed in the Jamadar studies, as well as new analytical methods to collapse and/or integrate a variety of data types into relevant risk models would facilitate larger, hypothesis-free analyses of neurobehavioral disorders.

In addition to accounting for the shear amount of data accumulated in imaging-genetics studies, specific consequences of rare and common genetic variation can complicate findings. Common variants typically have a relatively small, yet significant individual effect on phenotypes of interest, and identify genes and proteins fundamental to these processes. Many of these common variants reside in non-coding regions including miRNAs, long non-coding RNAs, and enhancer/silencer elements. Variation in these elements can have a substantial impact upon gene expression and function, as hypothesized with READ1 in *DCDC2*, which can lead to changes in neuroimaging and behavioral phenotypes. Small effect sizes require either a large number of subjects or a strong association to detect the relationship between phenotype and genetic marker. The need for large number of subjects could prove difficult in imaging studies due to costs and time investment, making large collaborative projects an attractive choice in the future. Recent studies have determined the importance of rare variants in common disease, particularly in neurobehavioral disorders such as autism spectrum disorders, intellectual disability, and bipolar disorder. These rare variants can be SNPs, usually in coding regions, or copy number variants, including deletions and duplications (e.g. 16p11.2 deletions and duplications). Although these rare variants appear to have a large effect size, the fact that they are rare can make it difficult to ascertain subjects or to make valid statistical conclusions due to sample size. Ensuring adequate size of comparison groups and screening for rare variation with the dwindling cost of DNA sequencing can allow for the use of both common and rare variants in examining neurobehavioral disorders using imaging, genetic, and behavioral data.

5. Conclusion

This review aimed to highlight the relatively new imaging-genetic studies of dyslexia and the promise this rising field has to unlock new insights behind the mechanisms and pathophysiology underlying this widely prevalent disorder. Although the field is immature, much has been learned regarding the possible downstream effects of dyslexia risk genes on brain structure, function, and circuitry. Current hypotheses into the underlying biology of dyslexia include: (1) risk genes leading to abnormalities to white/grey matter volumes and (2) risk genes disrupting brain activation patterns during reading-related tasks. These hypotheses appear to be rooted in aberrant neuronal migration, although other phenotypes including electrophysiological paradigms need to be explored. The future of imaging-genetics looks promising as more cohorts collecting a wide range of neurobehavioral, genetic, and imaging data start to become more widely available as has been seen in the ADNI and PING studies. Larger samples and new analytical strategies should reveal new mechanisms (genetic and imaging) that contribute to reading deficits in dyslexia. These insights will aid in the earlier detection of children with dyslexia and aid their overall academic and remediation potential.

Acknowledgments

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Highlights

Dyslexia is a complex, polygenic disorder affecting 5-17% of US schoolchildren.

Imaging-genetics aims to integrate neuroimaging, cognitive, and genetic data.

Imaging-genetics can identify novel risk genes and gene function in the brain.

The use of imaging-genetics will reveal new mechanisms of dyslexia.
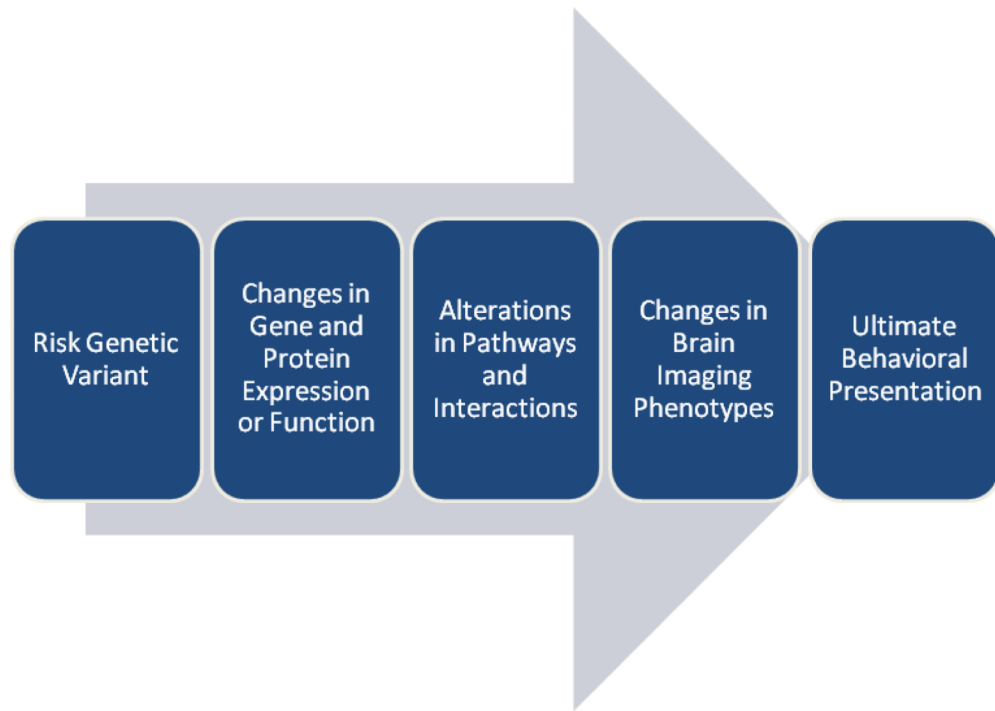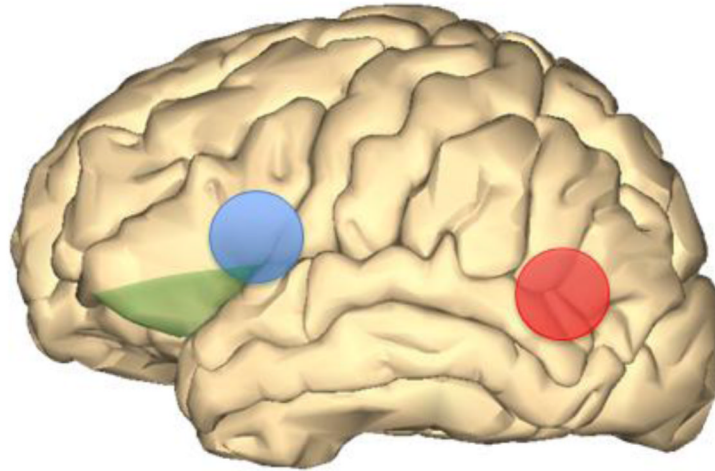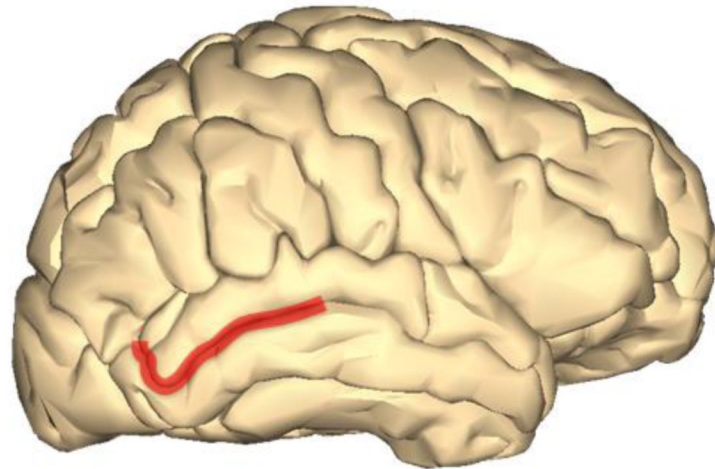
Figure 1.
The path from risk genetic variants to the ultimate clinical behavioral phenotype of impaired reading performance. Risk genetic variants lead to changes in the expression and/or functionality of genes and proteins. These changes in expression and function alter the performance and functionality of pathways and species that interact with the altered gene and protein. These fundamental changes in pathways and interactions alter brain imaging phenotypes in a gross level which then lead to the observed impairments in reading performance.
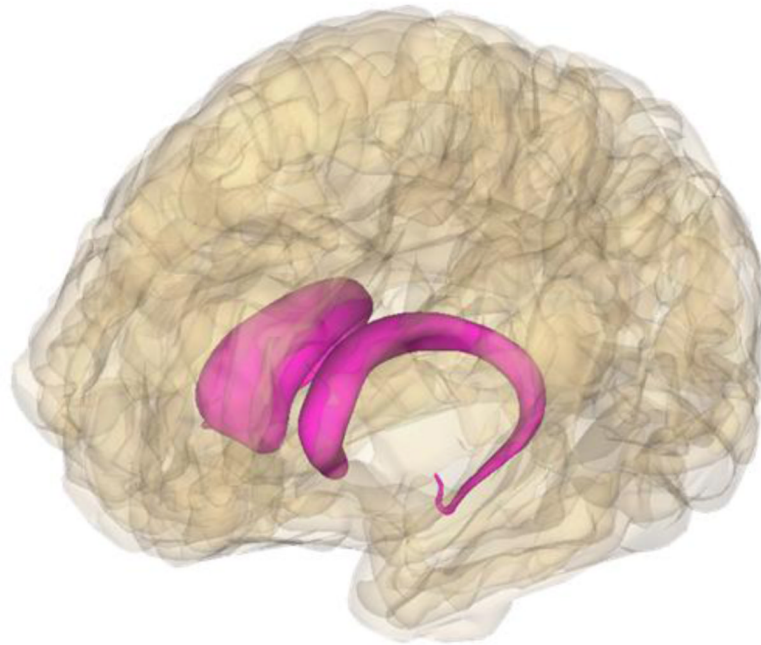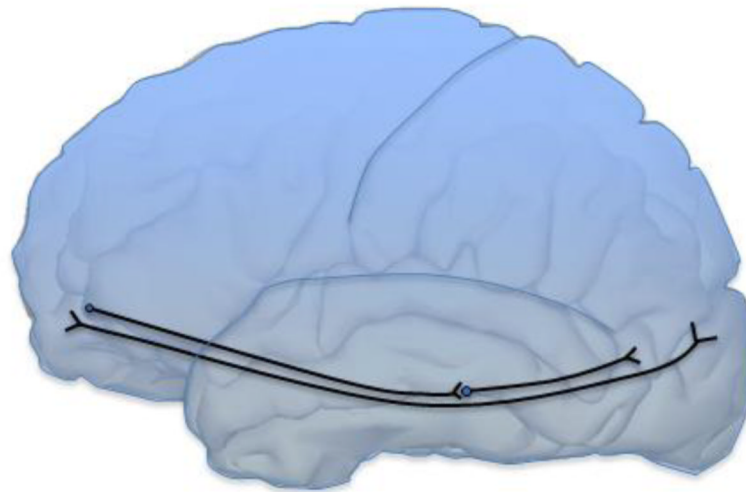
a

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Figure 2.
Brain models showing brain locations that displayed associations with dyslexia risk genes.
Images were generated using BodyParts3D/Anatomography service by DBCLS, Japan.
Figure 2a Left brain depicting Broca's area (blue), inferior frontal gyrus (green), and
temporo-parietal area (red) which all were associated with multiple dyslexia risk genes.
Figure 2b: *KIAA0319* showed specific loss of asymmetric activation of the right posterior
superior temporal sulcus.
Figure 2c: *FOXP2* showed associations with grey matter and activation in the caudate
nucleus.

Figure 2d: *CNTNAP2* showed association with the inferior fronto-occipito fasciculus (IFOF), which connects two main language areas: the inferior frontal gyrus and temporo-parietal area.
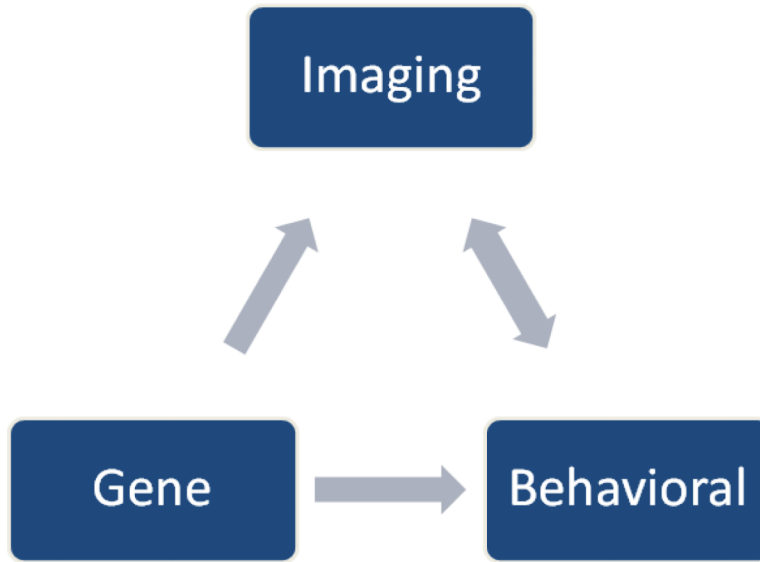
Figure 3.
A schematic of the relationship between gene, behavior, and imaging, in which neuroimaging measures are a mediatory step between risk genetic variants and the ultimate neurobehavioral phenotype.

Table 1

Nine dyslexia (DYX) loci identified by genetic analyses

Locus	Location	Candidate Genes	Locus Replicated?	Imaging-Genetics?
DYX1	15q21.3	*DYX1C1, CYP19A1*	Yes	Yes
DYX2	6p22	*DCDC2, KIAA0319, TTRAP, THEM2*	Yes	Yes
DYX3	2p16-p15	*C2orf3/MRPL19*	Yes	Yes
DYX4	6q13-16.2	N/A	Yes	No
DYX5	3p12-q13	*ROBO1*	Yes	No
DYX6	18p11.2	N/A	Yes	No
DYX7	11p15.5	*DRD4*	No	No
DYX8	1p36-p34	*KIAA0319L*	Yes	No
DYX9	Xq27.3	N/A	No	No

Table 2

Imaging techniques used in imaging-genetics studies of dyslexia

Technique	What it measures	Genes	References
Structural Magnetic Resonance Imaging (MRI)	Volume and thickness of cerebral regions, including grey and white matter volumes	*DCDC2* *KIAA0319* *FOXP2* *CNTNAP2* *DYX1C1* *C2orf3/MRPL19*	Meda et al.[81] Jamadar et al.[85] Darki et al.[86] Belton et al.[113] Watkins et al.[114] Vargha-Khadem et al.[115] Tan et al.[131] Scerri et al.[20]
Functional magnetic resonance imaging (fMRI)	Blood-oxygen-level-dependent (BOLD) signal indicating neural activity patternings during reading-related tasks performed in scanner	*DCDC2* *KIAA0319* *FOXP2* *CNTNAP2*	Cope et al.[87] Pinel et al.[89] Liegeois et al.[116] Wilcke et al.[25] Scott-Zealand et al.[132] Whalley et al.[133]
Resting State functional magnetic resonance imaging	Blood-oxygen-level-dependent (BOLD) signal depicting blood flow indicating possible regional interactions and connections while not performing tasks	*KIAA0319* *DCDC2*	Jamadar et al.[88]
Fractional Anisotropy (FA)	Diffusion Tensor Imaging (DTI) by MRI to infer white-matter connectivity among various regions of the brain	*CNTNAP2*	Tan et al.[131]
Positron Emission Tomography (PET)	Measures 3 dimensional activity throughout the brain by detection of an injected radiotracer (e.g. glucose, neurotransmitter)	*FOXP2*	Vargha-Khadem et al.[115]

Table 3

Candidate genes examined in imaging-genetic studies of dyslexia

Gene	Location	Function	Imaging Techniques Performed	References
DCDC2	6p22	Neuronal Migration Cilia	MRI fMRI Resting State	Meda et al.[81] Jamadar et al.[85] Darki et al.[86] Cope et al.[87] Jamadar et al.[88]
KIAA0319	6p22	Neuronal Migration	MRI, fMRI Resting State	Jamadar et al.[85] Darki et al.[86] Jamadar et al.[88] Pinel et al.[89]
FOXP2	7q31	Transcriptional Regulation Neurogenesis	MRI fMRI PET	Belton et al.[113] Watkins et al.[114] Vargha-Khadem et al.[115] Pinel et al.[89] Liegeois et al.[116] Wilcke et al.[25]
CNTNAP2	7q35	Cell Adhesion Voltage Gated Channels	MRI fMRI FA	Tan et al.[131] Scott-Zealand et al.[132] Whalley et al.[133]
DYX1C1	15q21.3	Neuronal Migration Cilia	MRI	Jamadar et al.[85] Darki et al.[86]
C2orf3IMRPL19	2p11-q11.2	Unknown	MRI	Scerri et al.[20]