Review

iMedPub Journals
www.imedpub.com

Journal of Childhood & Developmental Disorders
ISSN 2472-1786

2017
Vol.3 No.4:21

DOI: 10.4172/2472-1786.100059

# Predicting Developmental Dyslexia: A Brief Review of Genetics, Language and the Brain

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**Received date:** Oct 04, 2017; **Accepted date:** Oct 24, 2017; **Published date:** Oct 27, 2017

**Citation:** Figuccio MJ (2017) Predicting Developmental Dyslexia: A Brief Review of Genetics, Language and the Brain. J Child Dev Disord. Vol 3. No 4: 21.



## Abstract

Learning to read is an essential life skill, yet many children struggle and may even fail to learn to read. Developmental dyslexia (DD) is a specific learning disorder characterized by deficits in reading and reading-related tasks. Even though early intervention is crucial for successful remediation, many children do not receive a diagnosis until second grade or later. Research has shown high heritability of DD. Additionally, a link has been established between early language abilities and the development of reading skills. Moreover, individuals with DD display differences in neural structures implicated in reading even prior to learning to read compared to their typically developing peers. The aim of this review is to identify genetic, language, and brain predictors of reading.

**Keywords:** Dyslexia; Psychopathology; Language impairment

**Abbreviations:** AD: Axial Diffusivity; DD: Developmental Dyslexia; FA: Fractional Anisotropy; RD: Radial Diffusivity.

## Introduction

Learning to read is one of the major milestones in a child's life, and is essential for scholastic achievement, and future employment. Nonetheless, many children struggle while learning to read, and as many as 11.6% percent of children are diagnosed with developmental dyslexia (DD) [1]. DD is a brain-based specific learning disability characterized by deficits in reading and reading-related skills, such as phonological awareness (the ability to manipulate phonemes, the smallest units of speech), spelling, and/or rapid visual/verbal manipulation of letters and/or words despite adequate intelligence [2]. Children with DD are often viewed by educators and peers as lazy or simply "acting out," and consequently may develop anxiety or other psychopathology [3]. Compared to their peers, not only are children with DD less likely to complete high school and/or college, but also are more likely to enter the juvenile justice system [4].

The dilemma is that even though early intervention is the gold standard of treatment, DD is typically not diagnosed until second or third grade [5]. Children essentially need to struggle and fail prior to the recognition and diagnosis of the fundamental disorder. However, recent data suggest that DD is highly heritable and that the majority of genes implicated in DD are also involved in neuronal migration and axonal development as well as neural activity in language-related brain structures [6-12]. The aim of this review is to shed light on genetic, language, and neural predictors of DD.

## Genetic Basis of Developmental Dyslexia

DD is highly heritable; estimates suggest that DD occurs in 65% of monozygotic twin boys and 63% in monozygotic twin girls [13]. A recent meta-analysis consisting of 420 children with DD reports that children with a first degree relative with DD have a 45% chance of also being diagnosed with DD [1]. A number of DD susceptibility genes have been identified, including DCDC2, DYX1CI, ROBO1, KIAA0319, and the majority of these genes play a role in neuronal migration and axonal development [14-17]. Experimental manipulation of these genes in rodent models results in localized gray matter malformations, such as ectopias, which result in atypical cortical connectivity [18]. Cortical ectopias have previously been shown in postmortem studies of adults with DD [19]. Furthermore, DCDC2 deletion in humans with DD has been linked to reduced fractional anisotropy (FA), a measure of fiber tract integrity, in the left arcuate fasciculus and the genu of the corpus callosum [20]. This is consistent with the notion that some factors causing DD are present prior to learning to read and possibly at birth.

## Language and Reading

Ample evidence suggests an intimate relationship between the development of DD and language impairment, which is

diagnosed when a child's language development lags behind his/her other cognitive skills despite exhibiting average or above-average nonverbal abilities [21]. In fact, a number of genes implicated in DD, DCDC2, KIAA0319, FOXP2, CNTNAP2, are also implicated in language impairment [22]. Furthermore, markers within KIAA0319, FOXP2, CNTNAP2, and ZNF385D may contribute to comorbid diagnoses of DD and language impairment [22].

A recent study examined the relationship between speech production, language, and literacy in children with and without a familial risk of DD [23]. Interestingly, speech production was more highly correlated with phonological processing in children with a familial risk of DD than controls. Children with a familial risk of DD displayed speech production deficits compared to control children. 45% of children with a familial risk of DD developed word reading deficits. Poor readers displayed weaknesses in language, phonological processing, and early literacy measures, but no deficits in speech production. This suggests that speech processing deficits may be a marker of familial risk, but is not associated with the manifestation of DD.

Impaired nonword repetition has been implicated in both in language disorders and DD. In 2011, Baird and colleagues set out to disentangle this relationship, and examined children who had language impairment or were siblings of children with language impairment [24]. Nonword repetition was impaired in children who currently or previously displayed language impairment. Reading, decoding, spelling and comprehension skills correlated severity of language impairment. Interestingly, nonword repetition differentiated children with language impairment with and without reading impairment (defined as deficits in decoding or spelling). The authors suggest nonword repetition may be a marker for language impairment that co-occurs with reading, spelling, and decoding deficits.

A recent meta-analysis reviews oral language deficits in children with a familial risk of DD [1]. Infants and toddlers with a familial risk of DD who are ultimately diagnosed with DD display poorer articulatory skills, vocabulary knowledge, and grammar than peers with a familial risk of DD who do not develop DD [1]. Preschoolers with a familial risk of DD who ultimately are diagnosed with DD display poorer auditory processing skills, letter knowledge, and reduced sensitivity to rapid auditory processing compared to at-risk peers who do not receive a diagnosis of DD [1]. Furthermore, at-risk preschoolers demonstrate poorer articulatory skills, vocabulary knowledge, and phonological processing skills than control children [1]. At-risk school-age children display reduced nonverbal vocabulary than control children [1]. Interestingly by school-age, deficits in articulatory accuracy, vocabulary knowledge, letter knowledge, and grammar are resolved in at-risk children [1]. At-risk children who are later diagnosed with DD still display deficits in vocabulary knowledge at school-age compared to peers [1].

Although there is an intimate link between language and reading abilities, not all children with language impairment are later diagnosed with DD. In 2009, Bishop and Hayiou-Thomas aimed to identify protective factors in children with language impairment without DD. Children with language impairment without DD display deficits in vocabulary knowledge, sentence comprehension, and memory for sentences [21]. Interestingly, rapid serial naming performance was within the normal range for children with language impairment but not DD [21]. It appears that the ability to name pictures and digits rapidly may serve as a protective factor in the development of DD.

## The Reading Brain

Imaging studies suggest that the reading circuit in typically developing individuals consists of two left lateralized posterior systems, one which is ventral and one which is dorsal [25]. The ventral component consists of the left lateral extrastriate areas and the occipitotemporal area; it is activated during word and pseudoword reading tasks. The dorsal system includes the angular gyrus in the inferior parietal lobule, and the posterior aspect of the superior temporal gyrus (Wernicke's area); it is implicated in mapping the sounds of language (phonemes) onto printed text (graphemes). A third component, the anterior circuit consists of the inferior frontal gyrus (Broca's area); it is crucial for sequencing and control of speech-gestural recoding and is implicated in silent reading and naming [25].

## The Neural Basis of Developmental Dyslexia

Children and adults with DD display both structural and functional anomalies. Linkersdörfer and colleagues (2012) conducted a meta-analysis of nine VBM studies of children and adults with DD, and observed that the largest reduction in cortical grey matter was in the left fusiform extending into the left inferior temporal gyrus in readers with DD [26]. Additional reductions in grey matter were seen bilaterally in the supramarginal gyri and cerebellum in individuals with DD. Children with DD also show atypical activations when engaged in reading tasks. The temporoparietal region has been reported to have atypical functional activation, as measured with functional magnetic resonance imaging (fMRI), in DD compared to typical readers [27-30]. Reduced bilateral occipitotemporal activation was also observed in a meta-analysis of children with DD [31]. Additionally, older children and adults with DD also display increased right hemispheric activity during reading and reading-related tasks compared to controls [32]. The absence of activation differences in frontal and right hemisphere regions between typically developing and children with DD may suggest that these differences, often found in adults, reflect compensatory strategies.

School-age children and adults with DD also display altered white matter connectivity. Diffusion-weighted imaging (DWI) is a structural magnetic resonance imaging technique, which permits reconstruction and measurement of white matter tract integrity. Compared to typical adult readers, those with DD display reduced FA, a summary measure of white matter fiber architecture, in the left temporoparietal area [33-35]. FA is the normalized standard deviation of the three eigenvalues

and indicates the degree to which the isodiffusion ellipsoid is anisotropic (i.e., one or two eigenvalues are larger than the mean of all three eigenvalues) [36].

## The Role of the Arcuate Fasciculus in Reading and Developmental Dyslexia

The left arcuate fasciculus is a white matter tract that directly connects two well-documented regions of the reading network, the temporoparietal region and the left inferior frontal gyrus [37,38]. Intraoperative subcortical stimulation of the left arcuate fasciculus in adults resulted in phonemic paraphasias (i.e., incorrect substitution of phonemes) [39], and stroke patients with lesions in the left arcuate fasciculus also experience phonological deficits [40].

The left arcuate fasciculus is implicated in reading and reading related tasks including phonological processing, reading fluency, speech production, language comprehension, and speech repetition [41,42]. In fact, learning to read results in increased integrity of the left arcuate fasciculus in previously illiterate adults [43].

Vandermosten and colleagues (2012) segmented the left arcuate fasciculus into three regions: arcuate fasciculus-anterior, arcuate fasciculus-direct, and arcuate fasciculus-posterior in 20 adults with DD and 20 controls [38]. When compared to controls, adults with DD displayed reduced FA within the left arcuate fasciculus-direct. In addition to assessing FA, Vandermosten et al. also measured axial diffusivity (AD) and radial diffusivity (RD) [38]. AD measures the magnitude of microstructure oriented in the direction of the principal axis, while RD measures the magnitude of microstructure in the direction perpendicular to the principal axis [37]. Reductions in FA were accompanied by increases in RD, but not AD, which they interpreted as suggesting reduced myelination in adults with DD. Furthermore, they observed that the left arcuate fasciculus-direct, the midsection of the arcuate fasciculus, was positively correlated with phonemic awareness skills across groups. They also found a negative correlation between the FA of the right arcuate fasciculus-direct and phonemic awareness skills suggesting increased left lateralization in the arcuate fasciculus-direct is associated with enhanced phonological processing abilities.

Adults and children with DD display reduced FA within the left arcuate fasciculus relative to typically developing readers [33,38,44]. FA of the entire left arcuate fasciculus also correlates with phonological awareness in school-age children [36], and the volume of the left arcuate fasciculus correlates with phonological awareness in kindergarteners [45]. Furthermore, in a sample of 58 children between ages 5-9, white matter volume changes within the left arcuate fasciculus predict reading outcomes during the developmental period when children become fluent readers [46]. Similarly, the volume of the left arcuate fasciculus and superior corona radiata assessed in 38 children between five- and six-years predicted third grade reading abilities [47].

A recent study observed FA of the left arcuate fasciculus and bilateral inferior fronto-occiptial fasciculi correlates with phonological awareness in Dutch speaking pre-readers with (N=36) and without a familial risk of DD (N=35) [48]. Children completed behavioral testing at the start of kindergarten and an MRI scan at the end of the academic year. Children can be considered pre-readers since none of the participating schools included reading instruction in kindergarten. Regression analyses suggest phonological awareness skills predict FA in left arcuate fasciculus and bilateral inferior fronto-occiptial fasciculi across pre-readers with and without a familial risk of DD. Moreover, pre-readers with a familial risk of DD display reduced FA in the left inferior fronto-occiptial fasciculus and a trend toward reduced FA in the posterior left arcuate fasciculus compared to pre-readers without a familial risk of DD.

## The Role of the Corpus Callosum in Reading and Developmental Dyslexia

Even though a number of studies indicate atypical white matter connectivity in DD, the corpus callosum, the largest interhemispheric white matter tract remains understudied [49]. The corpus callosum may be a particularly important neural pathway in DD since children and adults with DD likely need to rely on the corpus callosum to recruit right hemisphere homologs during reading and reading-related tasks as a compensatory mechanism [33,50-53].

The corpus callosum's role in DD is complex due to its diverse morphology. The midbody of the corpus callosum is implicated in processing primary sensory and higher order auditory information along with premotor and primary motor cortices [54-56]. Large axons within the midbody of the corpus callosum facilitate rapid sensory integration essential to perceive temporal cues in auditory and visual stimuli which are needed for phonological processing and ultimately fluent reading. Individuals with DD (which included 12 children, 3 adults, and 9 compensated adults) display reduced FA values within the midbody of the corpus callosum [57].

In contrast, posterior regions of the corpus callosum, such as the splenium display greater FA values in adults and children with DD than typically developing controls [49,58-60]. In typical development, the splenium consists of small densely packed axons; thus, splenium enlargement suggests a greater number of axons and greater interhemispheric connectivity [56]. Furthermore, compared to typically developing adults (N=18), individuals with DD (N=9) display increased FA and AD in the splenium [49]. In particular, only letter word identification was negatively correlated with FA and AD within the splenium across controls and readers with DD. Reduced splenium interhemispheric connectivity may suggest reduced connectivity between the ventral occipital areas through occipital interhemispheric callosal fibers, and may result in greater lateralization of orthographic processing. This is consistent with the fact that typically developing individuals show left lateralized activation of the ventral occipital area, near the so-called visual word form area [61], while individuals

with DD display bilateral activation of this area during reading [28].

Hasan and colleagues (2012) similarly observed that compared to controls (N=26), children and adolescents with DD (N=24) display increased FA in the splenium of the corpus callosum [60]. However, they observed that the posterior midbody of the corpus callosum was negatively correlated with measures of single word reading and reading comprehension. The authors argue that increases in myelination and/or axial integrity within the posterior midbody of the corpus callosum may enhance interhemispheric communication, which may reflect greater compensatory mechanisms in children and adults with DD. This is in line with previous work suggesting increased values of FA in the posterior aspect of the corpus callosum is associated with reduced lateralization of the left hemisphere [62].

Since the corpus callosum is a bilateral structure, damage to territory on either the left side of the brain (or restricted inputs to those regions from damage to regions that project to those areas), can change the number (or integrity) of fibers traveling to the right side of the brain. This suggests that DWI measures of the corpus callosum are to some extent a reflection of both the relative integrity of the origin and destination of the fibers, as well as differential degree of connectivity between the two sides. When the origin and receiving sides of the cortex are symmetric, one would presume that the degree of lateralization of function would be lowest.

It is sometimes claimed that increases of interhemispheric connectivity mediate recovery in a subgroup of individuals with DD by enhancing right hemispheric activation beyond normal levels. [28,49,56,57,63]. Since this hyperactivation is generally observed past infancy, it would be of interest to see whether enhanced corpus callosum connectivity is intrinsic in children and infants at risk of DD prior to the majority of reading development. If enhanced connectivity precedes compensation, in certain callosal areas, this would help to differentiate the roles of the corpus callosum in reading acquisition *vs.* its recovery.

## Conclusion

Learning to read is critical for an individual's future success, yet a significant proportion of children struggle while learning to read and are ultimately diagnosed with DD. Typically, children do not receive a diagnosis of DD until second or third grade, even though research suggests that early intervention is the gold standard of care [5,64]. Troubling is the fact that a number of predictors of reading are present early in a child's life. The aim of this review is to shed light on genetic, language, and neural predictors of reading. Future research is needed to determine the sensitivity and specificity of these measures such that treatment is made available to the individuals that will likely benefit most. The long-range goal of early recognition and diagnosis is that children will receive treatment at an early age when their brains are most plastic and responsive.

## Funding

This work was supported by a Summer Research Award from Farmingdale State College.

## Competing and Conflicting Interests

The author declares no conflict of interest related to this work.

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