Molecular Genetics and Metabolism 110 (2013) 201–212

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Imaging-genetics in dyslexia: Connecting risk genetic variants to brain neuroimaging and ultimately to reading impairments

John D. Eicher [a], Jeffrey R. Gruen [a,b,c,*]

[a] Department of Genetics, Yale University School of Medicine, New Haven, CT 06520, USA
[b] Department of Pediatrics, Yale University School of Medicine, New Haven, CT 06520, USA
[c] Investigative Medicine Program, Yale University School of Medicine, New Haven, CT 06520, USA

ARTICLE INFO

Article history:
Received 29 May 2013
Received in revised form 2 July 2013
Accepted 2 July 2013
Available online 17 July 2013

Keywords:
Dyslexia
Neuroimaging
Genetics
Imaging-genetics

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.

Contents

* Corresponding author at: Departments of Pediatrics, Genetics, and Investigative Medicine, Yale Child Health Research Center, Yale School of Medicine, PO Box 208064, New Haven, CT 06520, USA. Fax: +1 203 737 5972.
E-mail address: jeffrey.gruen@yale.edu (J.R. Gruen).

1096-7192/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.07.001

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 to 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.

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

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 as 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 (Fig. 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 at 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, *Caenorhabditis 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