Published in final edited form as:
Behav Genet. 2011 January ; 41(1): 1–5. doi:10.1007/s10519-010-9439-9.

Moving closer to a public health model of language and learning disabilities: The role of genetics and the search for etiologies

Brett Miller, PhD and **Peggy McCardle, PhD, MPH**[1]
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, US Dept. of Health and Human Services

Abstract

Continued progress in language and learning disabilities (LDs) research requires a renewed focused on issues of etiology. Genetics research forms a central tenet of such an agenda and is critical in clarifying relationships among oral language development, acquisition of literacy and mathematics, executive function skills, and comorbid conditions. For progress to be made, diversified efforts must continue to emphasize molecular and behavioral genetics (including quantitative genetics) approaches, in concert with multi-disciplinary and multi-modal projects, to provide an integrated understanding of the behavioral and biological manifestations of language and learning disabilities. Critically, increased efforts to include ethnic, socio-economic, and linguistic diverse participant samples across a range of developmental stages is required to meet the public health needs of learners in the US and across the world. Taken together, this body of work will continue to enhance our understanding of LDs and help us move toward a truly prevention based approach to language and learning disabilities.

Identifying the underlying etiologies of learning disabilities remains central to scientific agendas focused on learning disabilities. This pursuit promises to inform our most basic understanding of what constitutes a learning disability (LD) as well as what constitutes risk or susceptibility for developing LD. We argue that understanding of genetic risk for LD is a necessary step to integrating our understanding of LD across scientific perspectives (e.g., genetics, neurobiology and behavior) with the important end goal of improving the lives of children with or at risk for LDs as well as those of youth and adults with LD. These interconnections already exist in many ways, given that, based on our behavioral definitions of LD, examining the associated genetics necessitates a multidisciplinary approach. Additionally, in the area of literacy, which is the predominant focus in this group of papers, molecular and behavioral genetics approaches can help the scientific field to move toward unified approaches to understanding the relationships among reading, writing, spelling, language development, and comorbid conditions.

Tackling the issue of etiologies has been a central concern of the two authors, who serve as program officials at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the US National Institutes of Health. Our portfolios, complemented by research supported by the National Institute on Deafness and Other Communication Disorders and the National Institute of Neurological Disorders and Stroke, focus on literacy and language development and disorders across the lifespan and in diverse

Correspondence concerning this article should be addressed to Brett Miller, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd., Suite 4B05, MSC 7510, Bethesda, MD 20892. millerbre@mail.nih.gov.

[1]The opinions and assertions presented in this paper are those of the authors and do not purport to represent those of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institutes of Health, or the U.S. Department of Health and Human Services.

populations. Although administratively separate, these NICHD portfolios are scientifically complementary and integrated by design. One portfolio focuses on literacy (reading and writing) and related learning disabilities. This program includes a focus on typical and atypical development of literacy skills and on learning disabilities that impact these skills; the relation of oral language development to these skills is integrated within the portfolio itself. The second program focuses on normative language development, development of biliteracy and bilingualism. In this portfolio, literacy development is integrated particularly with the focus on English language learners and more generally on the development of biliteracy skills. Common to both portfolios is a focus on examining the questions through a developmental lens across the lifespan. Scientific scope and goals between programs is coordinated and the staff work hand in hand on broader literacy goals of the NICHD. This integration allows for cross-disciplinary and topical inquiries that unite disparate or once disparate areas of science. Genetics is one theme that ties the issues of etiology, comorbidity and risk/resilience across portfolios.

The concept of risk is a central one when examining issues of specific learning disabilities. Often, we conceptualize risk based upon environmental factors that put children at a disadvantage when entering school (e.g., specific language impairment); we also identify risk through within school examinations of performance in key domains such as phonological awareness skills for reading. In the best cases, researchers and teachers are proactively monitoring performance in a range of domains related to speech and language development more generally as well as literacy, and using this information to inform decisions about the frequency of progress monitoring as well as the nature of the interventions proposed. At worst, they are waiting until children actually manifest learning difficulties or disabilities and then responding; although the response may still be reasonably timely, thinking of risk in the sense of genetic conveyance provides an opportunity for truly proactive educational and clinical interventions. The basic premise, described in part in this thematic issue and by others (e.g., Olson, Byrne, & Samuelsson, 2009; Petrill & Justice, 2007; Rice, Smith, & Gayán, 2009; Smith et al., 2010), is that genetic determinations of risk could inform early intervention efforts for children at risk for developing LD. Although it seems apparent that risk for LDs are mulitgenetic rather than single gene disorders, and even such multi-genetic risk clearly does not presuppose that a child will have LD, it may offer a reasonable signal to suggest preventive actions: that is, that we should monitor the child's progress in key skill areas frequently and be ready to intervene early and intensively to help prevent learning difficulties whenever possible or to help facilitate high levels of skill attainment for these individuals. We have known for some time, with some of the most compelling data provided by twin and family studies, that the relatives of probands (e.g., children of parents) with LDs are at higher risk for developing LDs themselves (see for example, Defries & Alarcon, 1996; Grigorenko, 2001; Kovas et al., 2007; Olson et al., 1999; Olson & Gayán, 2001; Pennington, 1999; Vellutino et al, 2004). Moving toward a model where genetic and environmental risk can signal the need for early, intensive intervention should help us support the needs of children more effectively.

Genetics research provides a unique window to examining common and separable factors that may link literacy and oral language skills and disorders (see, e.g. Newbury et al., and Bates et al., this issue) as well as other learning domains such as mathematics (Marino et al.; Docherty, Kovas, & Plomin, this issue). Although it is very likely not the underlying intent, educational leaders and policymakers often discuss reading in isolation of other factors that may have an influence on its development, particularly oral language and writing development. Thoughtful and clearly presented dissemination of findings and continued attention to multi-method, multi-disciplinary research that includes genetic, behavioral and potentially neurobiological research components is crucial. Such dissemination efforts can continue to highlight the accumulation of data suggesting meaningful links between the

development of these skills over the developmental timespan (Fisher & DeFries, 2002; Vellutino et al., 2004; Olson, Byrne, & Samuelson, 2009; Olson et al., 1999; Olson & Gayán, 2001; Plomin et al., 2008; Plomin, Kovas, & Haworth, 2007; Pugh & McCardle, 2009). Through the inclusion of broader measures of learning, such as measures of components of literacy, oral language development, executive functions skills, and math learning, we as a field can help elucidate the linkages among these areas, to the benefit of the research, practice, and policy communities (Cutting & Scarborough, 2006; Scarborough, 2005).

Continued inclusion of multiple perspectives within the genetics community will be increasingly important, as parallel efforts focused on genome wide association studies (GWAS) as well as rare variant searches and behavioral or quantitative genetics approaches move forward. Although we should utilize GWAS approaches to identify new common variants that may impact LD, particularly with well characterized existing samples, we must also work to recruit new, large, highly diverse samples that can be utilized for GWAS; homogeneous subsets of these samples could also be used for rare variant searches. Continued consideration should be given to combining samples for analysis; procedural challenges to integration across samples containing different sets of collected behavioral data persist, particularly in cases where the existing assessments purported to measure the same domain do not necessarily map onto the same underlying construct or where phenotypic characterization varies substantively (Cutting & Scarborough, 2006; Keenan, Olson, & Betjemann, 2009). Although these challenges present some functional limitations to the research questions that one can pose, there remains significant value to such investigations, even in these cases. For instance, one way around the problem of assessments tapping constructs with unknown or potentially different latent characteristics is to move toward usage (or more serious consideration) of common core batteries that are used across studies. Decisions about inclusion in such batteries would be inherently challenging, but the benefit of direct comparability along with the flexibility to enhance one's battery through the use of complementary assessments would be a benefit. This type of an approach would help us to avoid some potential difficulties from assessment approaches where the latent variable structure is problematic or simply unknown.

Rare variant approaches hold out significant promise particularly in examining particular familial pedigrees or in concerted focus on more significantly impaired individuals (e.g., Barr et al.; Buonincontri et al.; Rubinstein et al.; and Svensson et al.; this issue). Although the genes identified through family pedigrees may not generalize to broader populations of impaired individuals, these variants may be more predominant in particular geographic, familial, or ethnic groups and looking ahead one could imagine a concerted effort to screen for the rare variants showing the most severe effects, for prevention and remediation purposes. Also, knowing the range of variants that impact LD, their location and to the extent possible the gene function can inform the underlying etiology of the condition. This approach can also be nicely paired with broader behavioral or biological indices such as Roeske et al. (this issue) examination of rare variants and their association to event related potentials (an electroencephalographic measure) in 200 children with dyslexia.

Additionally, behavioral genetics approaches continue to hold promise in elucidating the underlying etiologies of learning disabilities. These approaches have historically been instrumental, through the use of twin data and community samples, to demonstrate the heritability of learning disabilities such as reading and in clarifying the nature of the comorbidity with conditions such as ADHD (Willcut & Gaffney-Brown, 2004; Willcutt et al., 2004). In this case, research clarified that the nature of the comorbidity between ADHD and reading disability was strongest with the attention deficit/inattentive subtype (Ebejer et al., 2010). This effort must be met by a matched, continued focus on examining conditions

such as ADHD (e.g., see Bidwell et al., this issue; van Beijsterveldt et al., this issue) and math learning disabilities for their own merit; such efforts should help clarify existing etiological relationships and help clarify future targets as the field moves to examine complex constellations of comorbidities with reading disabilities and other conditions. Moving forward, this research provides an opportunity to dynamically investigate the genetic and environmental contributions to the development of a range of content specific (e.g., reading, mathematics) and general processing skills (e.g., executive function skills and problem solving) as well as to tease out the nature of the relationships between inter-related skills such as reading and writing and how these change or track together over time; much of this work is ongoing.

Finally, genetics' research perspectives have proven fruitful for targets of animal based models of learning disabilities. To illustrate, Galaburda and colleagues continue to investigate rodent models of early developmental changes that relate to aspects of dyslexia (e.g., Galaburda et al., In Press). This work has recently focused on examining dyslexia candidate gene and their role in development. To date, the genes examined through their models (*DYX1C1*, *KIAA0319*, and *DCDC2*) have all been implicated in abnormalities in neuronal migration (Chang et al., 2005; Hannula-Joupi et al., 2005; LoTurco, Wang, & Paramsivam, 2006; Rosen et al., 2007; Taipale et al., 2003; Wang et al., 2006; Wigg et al., 2004; see also Meng et al., 2011), providing converging evidence implicating neurobiological origins for dyslexia consistent with earlier human post-mortem examinations (Galaburda, et al., 1985). Part of the value of this work is the ability to help understand the manifestations of identified candidate genes in early development, to inform human models of dyslexia, and importantly in tandem with other data, to help unify research conducted across levels (e.g., behavior, genetics and neurobiology).

Despite increasingly progressive views toward LDs in the US and abroad, there remains a social stigma toward individuals with learning disabilities in some cultures (O'Hara, 2003). From a social empowerment perspective, our hope is that continued developmental work on etiologies of LD, using both genetic and neurobiological approaches, will help to convey a cultural understanding of learning disabilities as biologically grounded. The continued progression of research and the dissemination of findings in clear, coherent publications at both the scientific, practice, and lay levels, could provide tangible benefits in a host of ways: empowering community leaders to raise awareness of signs that children may have language or learning impairments and of available treatment resources; empowering parents and community members to seek out necessary resources for their children, thereby facilitating earlier detection and treatment of LD; and creating a culture of support for diversity in its broadest sense and raising expectations for all community members.

In order for research on the genetics of learning disabilities to have real, practical influences on all children, and to be generalizable to children throughout the US, we must study representative groups of children. Research must include children from a variety of backgrounds, from the various racial/ethnic groups that typify the US demographics, those cultural and linguistic groups of English learning students who represent our fastest growing component of the school age population, and include children across socio economic levels. These investigations should include samples both in the US and abroad to increase the relevance of the work on the broader world stage. (For examples, see the following papers in this issue: Barr et al., Bates et al., Buonincontri et al., Docherty et al., Marino, et al., Matsson et al., Newbury, et al., Roeske et al., Svensson et al, and Venkatesh et al.) and to inform our understanding of risk particularly for recent immigrants. We know that these factors may increase or decrease risk – and that environment can influence how and when genetic risk factors may manifest. But we do not know the specifics of how learning risk factors and risks for comorbid learning difficulties play out across the diverse subgroups that

make up the US population. Importantly, this focus on diverse learners must continue to extend internationally to include cross-linguistic research and bilingualism research, aiding in our understanding of how learning disabilities may manifest themselves differently depending upon aspects such as the structure of the native language(s). This work is critical to a broader public health mission, benefits learners both internationally and domestically in the US, and will be critical to meeting the needs of language learners across the globe. Research samples also must include a range of age groups, since we have seen that even when early intervention is provided, and is effective, not every child will be identified in time or will respond to an intervention with complete success. Indeed as the learning demands change and increase with growth and development, children who have responded well to early intervention may indeed need ongoing support and continued treatment, depending on the nature and severity of the LD. In addition, we do not yet have good indicators for all possible manifestations of LD, as is evidenced by recent data on late emerging reading disability (LERD), which makes its appearance after students have been progressing with apparent success in early reading (Catts et al., in review; Catts & Hogan, 2003; Cutting et al., 2008; Scarborough, 2001). LERD illustrates a broader need to understand how the manifestations of learning disabilities may change over the developmental course depending upon the demands on the learner and the presence of other comorbid conditions that may develop over time. Also, this developmental perspective will be critical when examining learning challenges and disabilities that manifest over somewhat different, but overlapping, time courses, particularly for those with multiple learning challenges.

Examinations of etiology will form the core of any research agenda on LDs. Such an agenda must include multi-disciplinary, multi-approach methods to examining these problems and should increasingly integrate across methods and research modalities. Genetics research forms a central part of this approach. However, to meet the needs of an increasingly diverse set of learners domestically and abroad, we must reinvigorate our efforts to look developmentally and include ethnically, economically, culturally, and linguistically diverse learners in our samples. Researchers, educators and policymakers need data to inform continued movement toward a true, prevention based approach to language and learning disabilities. An integrated research agenda including genetics, neurobiology and behavior will be necessary if we are to meet these goals; we have the capacity to act now.

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