Many Layers of Dyslexia: Gene Discovery is Just the Beginning

by Fumiko Hoeft, MD, PhD and Albert Galaburda, MD

Multiple issues, including genetic and environmental factors—*programmed or just by chance*—influence our behavior, cognitive abilities, character traits, how likely we are to have a disorder, and how our brains are organized. A wide range of environmental factors may include, but would not be limited to, exposure to hormones during pregnancy (prenatal influence), nutrition, exposure to toxins, infections, traumatic injury, parental care, home setting, peer relationships, school experience, and culture. In the case of academic achievement and learning disabilities (i.e., dyslexia), "internal environmental factors" (e.g., motivation, anxiety, depression) may also be important modifiers (see *Examiner*'s "Research Alert on Educational Neuroscience" in the July, 2014 issue - http://www.interdys.org/July2014_Education_Neuroscience.htm). How do all of these factors cause and influence dyslexia?

Non-genomic factors influence gene function

Traditionally, passing genomic information across generations (i.e., inheritance of DNA sequence) has been considered to be the key pathway by which traits such as dyslexia, or risks for developing dyslexia, are inherited. However, there is increasing evidence suggesting that non-genomic factors (e.g., epigenetic and environmental) are also capable of influencing gene function and modifying inheritance. The term ***epigenetics*** refers to factors that contribute to gene function without altering the structure of DNA (Riddihough & Zahn, 2010). Epigenetic effects occur throughout the life span and are influenced by age, lifestyle, and disease. Epigenetic effects also differ according to the sex of the child and whether the gene is received from the father or from the mother (***parent-of-origin effect***; Lawson, Cheverud, & Wolf, 2013). The best-known examples are Angelman and Prader-Willi syndromes, where the disorder looks so different when it is inherited from the mother or from the father that it gives rise to two different diagnoses—even though both result from the same gene mutation on chromosome 15. It has recently been suggested that many of the most complex normal and abnormal traits may show parent-of-origin effects (Mott et al., 2014).

The first molecular genetics study that examined the interaction between genes and environment on reading found that genomic effects of the gene *DYX1C1,* a ***candidate susceptibility gene*** shown to increase the risk for dyslexia, were dependent on environmental factors: maternal smoking during pregnancy, infant birth weight, and socio-economic status (Mascheretti et al., 2013). Further, the effect of one gene may depend not only on the environment but often also on its interaction with a large number of modifier genes—a phenomenon known as ***epistasis.*** These and many more factors are likely contributors to what is notoriously known amongst researchers as ***missing heritability***, where candidate risk genes explain very little of the heritability (about 0.5% of reading ability and disability; Meaburn, Harlaar, Craig, Schalkwyk, & Plomin, 2008) even though the overall heritability for reading ability and dyslexia is high (in the order of 41% to 74%; Grigorenko, 2004).The numbers don't "match up;" something beyond just gene structure is contributing to heritability (e.g., gene function), which is highly modifiable.

So, what does this all mean?

First, unfortunately, it will likely take longer than we had originally envisioned to understand the genetic and other complex biological mechanisms underlying reading acquisition and dyslexia. However, the genes in question, for instance, are highly conserved in evolution, so that some of their fundamental functions and interactions can be studied in animal models, which will speed up discovery. Some progress has already been made in this regard (Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Kere, 2014). Second, the aforementioned insights may be best understood within the Multifactorial Inheritance Model (Galton, 1897),[1] where genetic factors from both parents, as well as environmental factors and interaction among these, contribute to risk or act as protective factors and account for at least one important part of the missing heritability of reading ability. This model explains how reading ability within the general population fits under a bell-shaped "normal" curve, rather than a graph with two peaks (i.e., those who are good

[1] See also the Multiple Cognitive Deficit Model (Pennington, 2006), and the Intergenerational MDM (van Bergen, van der Leij, & de Jong, 2014).

readers and those who have dyslexia). It also explains that dyslexia is not 100% heritable and that there is variation in the degree of reading problems among children with dyslexia, even within the same family. Additionally, genes associated with dyslexia risk do not affect only phonological or even language systems (genetic effects on multiple systems is known as ***pleiotropy***), so we will need to understand what combination or combinations of brain systems need to be affected in order for dyslexia to emerge. Ultimately, we will need a multilevel understanding of reading and dyslexia that links research from molecules, brain circuits, cognitive functions, and behavior—in animals as well as in humans. Third, these findings encourage us to pay close attention to environmental and other epigenetic effects (e.g., maternal and paternal effects and sex of the child) to determine how they may alter the dyslexia risk. This may prove to be a fruitful avenue of research that extends prior work studying children with and without dyslexia, or children with and without a family history of reading problems.

Interestingly, many of these ideas and initial research findings in animal and human research were aired decades ago. For example, sex-differences in genetic and environmental transmission patterns of dyslexia, in genetic transmission of different component skills of reading, and in protective factors as well as prenatal influence are reported in a 1993 book that resulted from a meeting hosted by The Dyslexia Foundation, *Dyslexia and Development: Neurobiological Aspects of Extra-Ordinary Brains* (Albert Galaburda, 1993). Not surprisingly, there is a recent revival of interest in some of these older theories and findings using modern brain imaging technologies (e.g., Altarelli et al., 2013, 2014; Black et al., 2012). One potential avenue through which our field may advance may be to take an approach that integrates old ideas with new approaches: animal to human research, molecules to behavior, reading to non-reading skills, and risk to protective factors. Of course, this is easier said than done.

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