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Review

The molecular genetics and neurobiology of developmental dyslexia as model of a complex phenotype

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ABSTRACT

Among complex disorders, those concerning neuropsychiatric phenotypes involve particular challenges compared to disorders with more easily distinguished clinical signs and measures. One such common and unusually challenging phenotype to disentangle genetically is developmental dyslexia (DD), or reading disability, defined as the inability to learn to read and write for an otherwise normally intelligent child with normal senses and educational opportunity. There is presently ample evidence for the strongly biological etiology for DD, and a dozen susceptibility genes have been suggested. Many of these genes point to common but previously unsuspected biological mechanisms, such as neuronal migration and cilia functions. I discuss here the state-of-the-art in genomic and neurobiological aspects of DD research, starting with short general background to its history.

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1. Introduction

Developmental dyslexia (DD) is one of many often co-occurring learning disabilities, but typical of it is the stark contrast between a child's overall performance and the distinct problems in learning to read and write. An early description of DD by Bastian [1] has documented that nicely, but even though these authors made a distinction between developmental and acquired (e.g., following brain trauma), the often familial clustering waited for later documentation. Besides occasional notes in the early 1900's, first Norrie in 1939 (cited in [2]) reported familial clustering in nearly all cases, and Hallgren's study in 1950 [3] of 116 index individuals and 160 affected family members made a compelling case. Hallgren (1950) also suggested dominant inheritance as the most plausible mode of inheritance.

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Importantly, DD can occur in children with perfectly normal overall intellect, but in the past they were often unfortunately labeled as "backward" or "stupid" [4]. There is still room today for improvement for how schools and parents can recognize and diagnose DD early enough, get appropriate help and training for a child, and prevent the untoward feeling of being different and becoming socially handicapped. The goal should be to allow every child to reach his or her full individual intellectual potential.

Indeed, it is the specificity of the defect in learning that makes DD an unusually interesting phenotype to study and understand. But not only is DD interesting from the neuropsychological point of view; DD involves one of the very specific skills that distinguishes us humans from the other primates that cannot learn character-based coding and decoding. Unsurprisingly, there are likely common threads between language development and reading and writing, as many dyslexic children have a history of delayed language development as well. Looking beyond our species, the developmental mechanisms that have allowed language, reading and writing to evolve in humans are unlikely to be fundamentally different from mechanisms that may have been adapted to other tasks in other organisms. Thus, an understanding of the molecular and neurobiological mechanisms of DD might more generally also teach us something about cognition, the developmental processes of the brain, and the specific evolution of the human brain.

2. Evidence for biological background of DD

Even before the advent of genomic studies, multiple converging lines of evidence have suggested that DD has an early developmental and biological etiology. The familial occurrence with even apparent dominant patterns of inheritance suggested genetic background early on [2,3]. These studies have been expanded to observations on twins that have supported multifactorial genetic etiology rather than simple dominant inheritance in most cases [5]. Importantly, these studies have supported a strong genetic effect, reaching 70-80% for different reading and related measures, in contrast to modest classroom or other environmental effects. Specific loci have been mapped by genetic linkage methods in exceptionally large pedigrees, providing strong evidence of dominant gene effects in some families [6,7].

Other lines of evidence have studied brain event-related potentials in children of dyslexic parents. The results have indicated early biological effects already in newborn babies, long before reading and writing skills can develop [8] and further extended into associations to poor verbal memory skills at age 5 before the development of reading skills [9]. Again, the early onset of related problems lend support for the notion of biological rather than environmental influence at the bottom of DD.

Brain imaging approaches employing magnetic resonance imaging (MRI) found differences in white matter microstructure bilaterally in temporo-parietal regions between DD and normal readers [10]. Independent studies using positron emission tomography (PET) to measure brain activation patterns in DD and normal readers speaking different languages found common correlates in all [11]. More specifically, there were common brain areas activated in all individuals and particular areas in the left temporal and occipital gyri that were significantly less activated in DD than in normal readers. Interestingly, later PET studies involving Chinese participants using a logographic writing system found also brain areas with reduced activation in DD, but the areas were different from those using alphabetic writing [12].

Even though the biological correlates of brain structure and activation appear in the same anatomical regions irrespective of language, their differences necessitate emphasis on different aspects and measures for DD when testing children and establishing diagnostic criteria. The learning profiles for spelling and writing may be very different in highly orthographic languages (such as Finnish) in comparison to languages with irregular spelling (such as English or French). The variation in testing and diagnostic criteria obviously makes it more difficult to combine subjects from different countries, and may increase heterogeneity between study participants. Combined with genetic differences between populations, the cumbersome diagnostics, and heterogeneity of criteria may explain at least partially the lack of successful large-scale genetic association studies as of yet. Typically, such studies require beyond ten thousand participants to yield strong association results for genetic loci with modest risk effects.

Thus it may not be surprising that our knowledge of specific susceptibility genes in DD is still limited to such loci that have been implicated by single-gene strategies, such as genetic linkage studies in unusual large dominant families and subsequent targeted association studies as well as chromosome translocations or chromosomal deletions associated with individuals with DD. I will in the next paragraphs present the first susceptibility genes implicated in DD and follow them up with neurobiological, cell biological and neuroimaging data that have illuminated the possible biological mechanisms of DD.

The literature on the molecular genetics and neurobiology of DD is already so extensive that this review cannot cite all the relevant studies. The focus is kept on the identification and first implications of the first DD susceptibility genes. For complementary information on DD, the reader may look for other recent reviews [13,14].

3. Genetic linkage studies identified loci for dyslexia

The diagnosis of DD is not based on a simple laboratory test, but depends on the combination of personal history, assessment of cognitive skills, and sophisticated neuropsychological testing [15,16]. There is unquestionable variation in the degree of DD and also distinct phenotypic heterogeneity, both of which contribute to difficulties in designing and performing genetic studies.

As in many complex disorders, the first attempts to identify genetic loci influencing susceptibility were based on genetic linkage mapping in unusually large families with dominant inheritance patterns or multiple small families (introducing the risk of genetic heterogeneity). Table 1 lists those loci that have been recognized as replicated by the Human Gene Nomenclature Committee that has also named them as DYX1 through DYX9. It is worth noting that even though the genetic linkage studies have been based on families collected from different countries (and thus speaking different languages), the results of genetic mapping have been largely consistent.

In the early 2000's, these loci became also the targets of positional cloning studies with various strategies. The first candidate susceptibility genes for DD were identified based on studies of rare chromosomal translocations localizing within the implicated genetic loci on chromosome 15 (DYX1, gene DYX1C1) [17] and chromosome 3 (DYX5, gene ROBO1) [18]. Parallel efforts employed genetic fine-mapping based on assessing associations at increasing resolution, and yielded two candidate DD genes on chromosome 6 (DYX2, genes DCDC2 and KIAA0319) [19–22], chromosome 2 (DYX3, genes C2Orf3 and MRPL19) [23] and somewhat later on chromosome 18 (DYX6, genes MC5R, DYM and NEDD4L) [24,25]. A cluster of additional four genes was suggested on the basis of a submicroscopic deletion of chromosome 21 (genes PCNT2, DIP2A, S100B, and PRMT2) [26], even though this locus had not been previously recognized by genetic linkage studies. For many of the genetically linked loci, there is still no further evidence of specific genes, which may be explained either as the absence of fortuitous