

From genes to behavior in developmental dyslexia

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All four genes thus far linked to developmental dyslexia participate in brain development, and abnormalities in brain development are increasingly reported in dyslexia. Comparable abnormalities induced in young rodent brains cause auditory and cognitive deficits, underscoring the potential relevance of these brain changes to dyslexia. Our perspective on dyslexia is that some of the brain changes cause phonological processing abnormalities as well as auditory processing abnormalities; the latter, we speculate, resolve in a proportion of individuals during development, but contribute early on to the phonological disorder in dyslexia. Thus, we propose a tentative pathway between a genetic effect, developmental brain changes, and perceptual and cognitive deficits associated with dyslexia.

One goal of cognitive neuroscience should be to establish transparent pathways between genes and behavior and between genetic variants or mutations and behavioral disorders. This effort starts with the discovery of genes associated with a particular behavior, but must continue with the characterization of all the downstream steps to that behavior, which requires major, collaborative, cross-level research. Developmental dyslexia, a relatively common form of specific learning disability, is slowly giving way to this type of discovery. We can now propose a pathway, albeit still speculative and incomplete, between genetic variants (or gene functions) and a complex developmental behavioral disorder, with intervening abnormalities of brain development.

Following reports of acquired disorders of reading from injury affecting the occipital and parietal lobes, researchers looked for congenital anomalies involving those same posterior portions of the left hemisphere to explain developmental dyslexia¹. Subtle cortical neuronal migration anomalies were observed in several post-mortem brains². Findings consistent with congenital brain malformations were reported in a few cases of dyslexia and developmental language disorders. In one autopsy case³, for instance, abnormal cortical folding affected the

parietal lobes, and neuron number was high in the subcortical white matter. Magnetic resonance imaging identified 8 dyslexic cases with the neuronal migration anomaly periventricular nodular heterotopia⁴, and 13 children with perisylvian polymicrogyria (a form of abnormal neuronal migration) and developmental language deficits⁵.

The most consistent findings in the original cases² are nests of neurons, termed ectopias, in cortical layer 1 and occasional focal microgyria affecting language areas. Additional defects in the thalamus and cerebellum^{6,7}, together with the cortical changes, are proposed to explain the dyslexic phonological deficits, as well as the auditory discrimination and motor deficits that occur in some cases. Animal models were developed to study possible causal relationships between the brain abnormalities and behavior. However, the causes of the malformations in the dyslexic brain remained unclear until four candidate dyslexia susceptibility genes were reported—*DYX1C1*, *KIAA0319*, *DCDC2* and *ROBO1*—which are involved in neuronal migration and other developmental processes. Experimental interference with these genes leads to neuronal migration anomalies^{8–14}.

Cognitive phenotype of dyslexia

The defining symptom of developmental dyslexia is a severe and specific difficulty in reading acquisition that is unexpected in relation to other cognitive abilities and educational circumstances¹⁵. At the cognitive level, there is widespread agreement that a large majority of dyslexic children suffer from what is commonly termed a “phonological deficit,” that is, a deficit in some aspects of the mental representation and processing of speech sounds¹⁶. Evidence for this phonological deficit comes from three main behavioral symptoms: (1) poor phonological awareness—the ability to consciously pay attention to and mentally manipulate speech sounds, (2) poor verbal short-term memory—the ability to temporarily maintain phonological representations active, and (3) slow lexical retrieval—the ability to retrieve the phonological form of words for speech articulation^{17,18}.

Other behavioral symptoms are sometimes associated with dyslexia, including various types of auditory (prominently rapid auditory processing), visual and motor deficits. It is likely that purely visual (but not ocular) problems can explain reading disability in a minority of dyslexic children, although the various theories of visual dyslexia still need to be further specified and reconciled^{19,20}. The associated auditory and motor deficits are often proposed to be the underlying cause of the phonological deficit^{7,19,21}. However, their prevalence, at least in older children and adults, is too low to explain the phonological deficit in a straightforward way, and they are not specific to dyslexia^{7,22}. However, it could be argued that, as with most developmental disorders, constellations of symptoms change with maturation, with some symptoms remaining unchanged, others improving, and still others

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worsening, so that years later initial associations among symptoms, including causal relationships, are no longer detectable. Therefore, the possibility still exists that auditory deficits in the first year of life (or earlier?), beginning before or at the time when phonological structures are being established, may contribute to anomalies in phonological development. However, this hypothesis is still speculative in the absence of developmental studies beginning in infancy, focusing specifically on this question. This effort will be helped along if early detection of dyslexia susceptibility by genetic testing or by anatomical markers using state-of-the-art *in vivo* imaging can be reliably implemented.

Dyslexia commonly coexists with specific language impairment (SLI), developmental coordination disorder and dyscalculia, to name a few^{23–25}. This suggests at least partly shared etiological factors, for which neuroimaging and genetic data should be highly informative. For instance, it has been suggested²⁶ that the grey matter abnormalities observed in dyslexia partly overlap with those observed in SLI. Common genetic factors would also be expected, although no overlaps have as yet been detected.

Neural correlates support every observed cognitive deficit seen in dyslexia. Both cytoarchitectonic and larger-scale gray- and white-matter abnormalities in left perisylvian cortical areas involved in phonological processing provide a sound basis for the phonological deficit^{2,21}. The additional abnormalities in the thalamus and cerebellum provide equally sound bases for sensory and motor deficits^{6,7}. Animal modeling of these brain abnormalities (see below) indicates that they interact during development.

Cellular and molecular mechanisms

Familial occurrence and twin studies have long suggested a genetic basis for dyslexia. For over twenty years, it has been possible to pinpoint chromosomal sites related to dyslexia susceptibility (for example, refs. 27–29). *DYX1C1*, *KIAA0319*, *DCDC2* and *ROBO1* are reported to be dyslexia candidate susceptibility genes^{8–14}. The proteins encoded by these genes, though diverse, may be functionally linked, either directly or by virtue of their similarity to other proteins, in pathways involved in neuronal migration and axon growth. Developmental processes, such as neuronal migration and axon growth, share several features and requirements, including dependence on coordinated changes in cell adhesion and cytoskeletal restructuring. *ROBO1* has clear roles in axon growth and neuronal migration, and the proteins in the *DCX* family, of which *DCDC2* is a member, have well-documented involvement in neuronal migration to neocortex and may also be involved in the development of the corpus callosum. In addition, *KIAA0319* shares extracellular motifs with proteins involved in cell adhesion.

DCDC2 is one of an eleven-member group of proteins distinguished by the presence of tandem or single *dcx* domains. The first characterized gene of this family, *DCX*, was identified after the discovery of mutations in a gene that cause double cortex syndrome and lissencephaly in humans^{30,31}. Another member of the *DCX* family, *DclK*, genetically interacts with *Dcx* in mice, and two functioning copies of *Dcx* and *DclK* are necessary both for growth of axons across the corpus callosum and for neuronal migration in cerebral cortex^{32,33}. *Dcdc2* has not yet been tested directly for a possible role in axon growth across the callosum. However, as with *DclK* and *Dcx*, local loss of function induced by RNAi of *Dcdc2* results in the interruption of normal neuronal migration in neocortex (Fig. 1)¹². A comparison of the biochemical and cellular functions of proteins in the *DCX* family³⁴ shows that *DCDC2* shares functional features with *DCAMK1* (also known as *DCLK*) and *DCX*.

KIAA0319 is the second of the two candidate dyslexia susceptibility genes on chromosome 6p (refs. 10,11). The gene codes for an integral membrane protein with a large extracellular domain, a single trans-

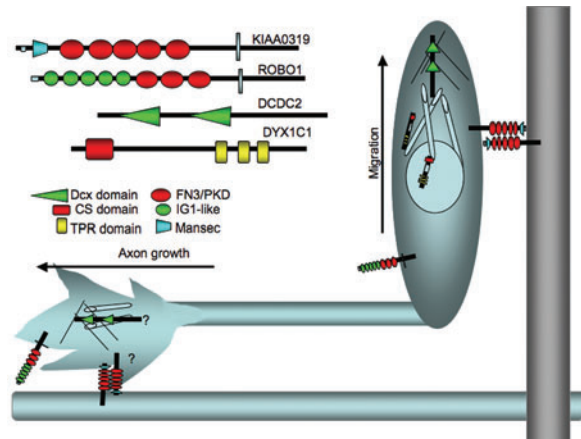


Figure 1 Protein domains and possible functions. *KIAA0319* and *ROBO1* serve as transmembrane adhesion molecules and receptors that guide axons to appropriate targets. *DCDC2*, and perhaps *DYX1C1*, are proposed to act as downstream targets that then serve to modulate changes in cytoskeletal dynamic processes involved in the motility of developing neurons. Critical future studies must now address whether there are links between the functions of these proteins in migration and axonal pathfinding.

membrane domain and a small intracellular C-terminus. One protein—polycystin 1—with a similar extracellular domain, is involved in adhesion between kidney cells. A role in cellular adhesion for *KIAA0319*, or its homolog in rodents, has not yet been directly tested. However, the phenotype in RNAi studies in developing brain indicates a role for *KIAA0319* in neuronal migration, perhaps by changing the relationship between migrating neurons and radial glia¹¹. The change in association between radial glia and migrating neurons following interference with the mouse homologue of *Kiaa0319* (called D130043K22Rik) is suggestive of a change in adhesion between migrating neurons and radial glial fibers.

ROBO1 and *DYX1C1* were both identified as candidate dyslexia susceptibility genes from chromosomal translocations in small pedigrees or by linkage disequilibrium association studies^{9,13,35}. The functional alleles that initially implicated *DYX1C1* in dyslexia do not significantly associate with reading disorders in other, larger populations, calling into question the general relevance of these *DYX1C1* alleles to dyslexia (for example, refs. 36,37). The domain structure of *DYX1C1* does not clearly link it to cell adhesion or to cytoskeletal dynamics. However, *in vivo* RNAi studies indicate that it is involved in neuronal migration^{14,38}. Soon after transfection, neurons expressing the interfering construct are arrested in the intermediate zone, and by adult life, many of them have migrated, albeit late, and have achieved abnormal laminar placement. Additional neurons have migrated through breaches in the basal lamina to produce ectopias in the molecular layer, which resembles the picture seen in post-mortem dyslexic brains (Fig. 2).

The role of invertebrate and vertebrate homologues of *ROBO1* in neuronal development is well understood. Initially found in a genetic screen for axon-patterning mutants in *Drosophila*, the roundabout gene and vertebrate homologs are important in axon growth across the commissures in the brain and spinal cord^{39,40}. The ligands of *ROBO* proteins—slits—have been implicated in both axon growth and cell migration. For example, slit directs the migration of neurons to neocortex by repelling cells away from the proliferative zones—the ventricular zone and ganglionic eminence—of the developing forebrain⁴¹. Despite this exciting beginning, we want to stress that the functional significance of the specific genetic variants of the four genes associated with

dyslexia in humans has not yet been established. None of these genetic variants consistently linked with dyslexia are mutations in the coding sequences of the genes, and, therefore, it is possible that they result in changes in the spatial or temporal pattern of expression, decreases in expression, increases in expression, or perhaps even no change in expression in developing or mature human brain. The *KIAA0319* allele linked with dyslexia results in a 40% decrease in expression in *in vitro* assays¹¹, but it is not yet known whether this translates into a similar decrease in either the developing or mature brain. A major challenge for future studies, therefore, will be to link the specific genetic variants associated with dyslexia to specific changes in function in developing and mature human brain. Parallel animal studies will be essential to reveal the causal chain of events that connects developmental perturbations resulting from interference in the expression of these genes to changes in cortical circuitry, function and, ultimately, behavior.

Animal models

Animal experiments have aimed at reproducing the anatomical findings made in post-mortem dyslexic brains in order to study their detailed structure and physiology and possible causal relationships to behavior². Principally, these models have mimicked focal microgyria and molecular layer ectopias (Fig. 2). Induction of microgyria in male and female rats leads to local changes in cortico-cortical connectivity and changes of connectivity across the corpus callosum. Microgyria induction also results in thalamic changes in male rats, which are similar to those found in dyslexic thalami, whereas comparable interventions in female rats do not. This finding uncovered a developmental plasticity difference in the two sexes that may help explain the common sex differences, in which more males are affected by developmental disorders^{6,42,43}. Perinatal exposure of rats with induced microgyria to testosterone propionate is capable of triggering in females the same thalamic changes seen in males, although the same manipulation does not change the microgyria itself. The thalamic changes are associated with auditory perceptual deficits in the males, which suggests maladaptive plasticity leading to the establishment of anomalous cortico-thalamic circuits following early cortical insult. To explain the male predominance in many developmental language disorders, it has been claimed that males are more vulnerable to early brain injury. However, the difference between the sexes may also be in the response to early injury⁴⁴.

Abnormal behavior results from induction of the above-mentioned cortical malformations in neonatal rats. This is surprising, considering that the malformations themselves are distinctly small, which probably reflects the underlying cortical and thalamic changes that follow malformation induction. Both rats with induced microgyria and mutant mice that spontaneously develop neocortical ectopias show behavioral deficits⁴⁵. NZB/BINJ mice with ectopias perform poorly in a non-spatial discrimination test as well as in a spatial water escape maze. In some cases, animals with ectopias from different strains, with different locations for their ectopias, perform discrepantly on some tests. For example, BXSb/MpJ ectopic animals learn the Lashley III maze well, whereas NZB/BINJ mice do not. The former have ectopias in frontal cortex, whereas the latter have them in parietal cortex. On the other hand, on two tests of working memory, one involving an inverted Lashley III maze, the other a delayed-match-to-sample task, ectopic BXSb/MpJ mice performed poorly. In sharp contrast, these same mice were superior in learning a reference memory spatial water maze. Both sets of findings could be related to their frontal cortical pathology, a known part of the working memory circuit. On some of these tests, deficits seem to interact with paw preference. Ectopias or microgyria induced in normal mice cause similar behavioral deficits⁴⁶. Lesioned mice (irrespective of hemisphere or type of damage) perform poorly when compared to sham-operated

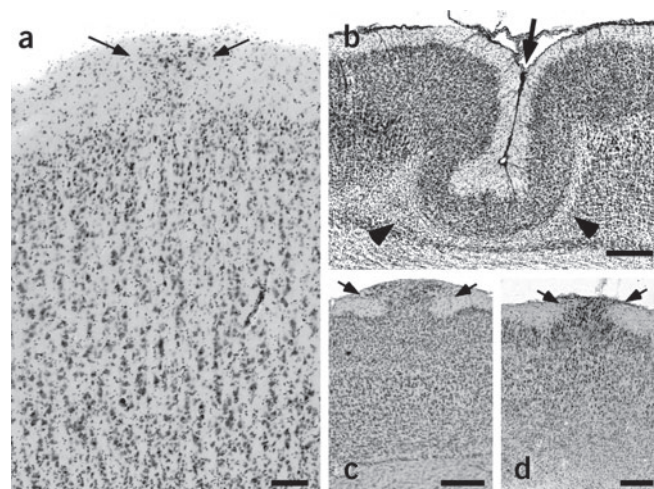


Figure 2 Human and animal neocortical malformations. (a) Molecular layer ectopia (arrows) in neocortical layer I of a human dyslexic. Scale bar, 100 μm . (b) Induced microgyria in a rat. This malformation, induced by placing a freezing probe onto the skull of a newborn rat, is generally characterized by the presence of a microsulcus (arrow) and a lamina dissecans (arrowheads). Scale bar, 300 μm . (c) Spontaneous molecular layer ectopia (arrows) in an immune-defective mouse. Scale bar, 250 μm . (d) Molecular layer ectopia (arrows) induced in a rat by *in utero* electroporation of RNAi targeted against *Dyx1c1*. Scale bar, 250 μm .

animals in discrimination learning, in a spatial Morris Maze match-to-sample task, and in a Lashley Type III maze. In sum, spontaneously arising or induced neuronal migration anomalies in the rodent cortex give rise to a range of cognitive deficits in these animals, even though the injury causing these malformation is limited in scope.

The discovery that phonological difficulties in language-disabled individuals may sometimes be accompanied by deficits in rapid auditory processing provided an additional avenue for the use of animal models in the study of human language disabilities. Focal cortical malformations, similar to those seen in the postmortem brains of human dyslexics, are associated with rapid auditory processing deficits in rodent models^{47–49}. Male rats with induced focal microgyria are unable to perform a 2-tone discrimination task when the stimulus duration is relatively short. In contrast, sham animals and microgyric females perform well at all stimulus durations. Deficits are larger in juvenile than in adult animals⁴⁷, and the cognitive demand of a particular task predicts the acoustic threshold at which deficits can be elicited. For example, young animals with cortical malformations show processing deficits on relatively simple gap-detection threshold tasks, whereas more complex tasks such as two-tone sequence or FM sweep discrimination are typically required to elicit deficits in adult animals with malformations. Notably, these patterns seem to parallel population trends in human language-disabled populations, with young males being particularly at risk⁴². What is certain so far in the lesion model of developmental cortical malformations is that behavioral and anatomical abnormalities in manipulated animals vary according to age and sex, and that some of the behaviors correlate with changes in the thalamus, whereas others are more likely the result of changes in cortico-cortical circuits. As this seems also to be the general situation in developmental language disorders such as dyslexia, it would be reasonable to expect that, although both phonological and auditory processing deficits could be demonstrated in many dyslexics, in others the latter deficit may improve with age and thus be undetectable at the time of dyslexia diagnosis. In

still others, auditory processing deficits would remain in the face of improved phonological problems, leading to a diagnosis other than dyslexia. In the present state of knowledge, it would be most prudent to state that the variety of behavioral deficits in dyslexia have a common underlying genetic and brain developmental cause, and any causal relationships among perceptual and linguistic deficits will need demonstration by appropriate, developmentally designed human studies.

The focus of animal modeling in dyslexia research is now apt to change with the introduction of candidate dyslexia susceptibility genes into the research armamentarium. Many of the findings in the injury-induced cortical malformation—cortical and thalamic changes, changes in connectivity, associated temporal auditory processing and cognitive deficits, age and sex effects—will need to be replicated using genetic models. Future experiments will need to answer questions that were not relevant in the injury models, but are important for the genetic theory of dyslexia. For instance, a challenge will be to show how variant gene function affecting a brain development gene can result in exquisitely focal anatomical and behavioral phenotypes to explain the anatomical anomalies and behavioral deficits in dyslexia. Yet, is the effect as focal as we think, or is it more widespread at the initial state before plasticity and recovery remodels the brain from the initial event? The discovery of candidate dyslexia susceptibility genes provides both a challenge and opportunity to better understand this specific developmental learning disorder. We hope that our understanding of other developmental learning disorders will also benefit from this approach.

Conclusions

Our perspective on the state of the art in dyslexia research, as illustrated in this abridged review of the extensive literature on developmental dyslexia, is that variant function in any of a number of genes involved in cortical development, including but probably not restricted to the known candidate dyslexia susceptibility genes *DYX1C1*, *KIAA0319*, *DCDC2* and *ROBO1*, can be responsible for subtle cortical malformations involving neuronal migration and axon growth, which in turn leads to abnormal cortico-cortical and cortico-thalamic circuits that affect sensorimotor, perceptual and cognitive processes critical for learning. Plasticity relating to the initial cortical developmental events triggered by the aberrant gene function vary with respect to age and sex, resulting in individual differences in the adult behavioral phenotype. Ongoing work is focused on the initial molecular events leading to the neuronal migration anomalies associated with the candidate dyslexia susceptibility genes, the developmental plasticity associated with the initial event, and the detailed nature of the resulting sensorimotor, perceptual, cognitive and behavioral disorders.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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