fimp
Federazione Italiana
Medici Pediatri

Società Italiana di Pediatria Preventiva e Sociale
SIPPS

FIMPAGGIORNA *2008*

IL PEDIATRA TRA ANTICHI PROBLEMI E NUOVE ACQUISIZIONI IN TEMA DI….

DISLESSIA

Ennio Del Giudice

Dipartimento di Pediatria, Settore di Neuropsichiatria Infantile
Università degli Studi di Napoli "Federico II"

Comparsa dell'uomo e della scrittura

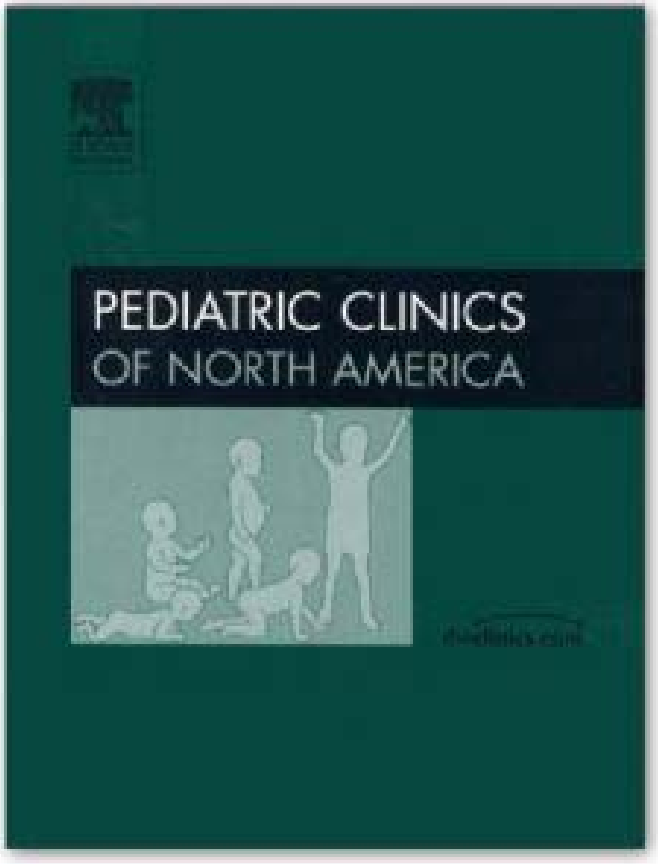
La comparsa e la diffusione dell'uomo

- *Australopithecus*
  4 milioni di anni
- *Homo erectus*
  ~ 2 milioni di anni
- *Homo sapiens*
  500.000 anni
- *Homo sapiens sapiens*
  ~ 40.000 anni

La nascita della scrittura

- Scrittura ideografica
  ~3100 a.C.
- Scrittura fonetica alfabetica ~1500 a. C.

L’interesse per il pediatra

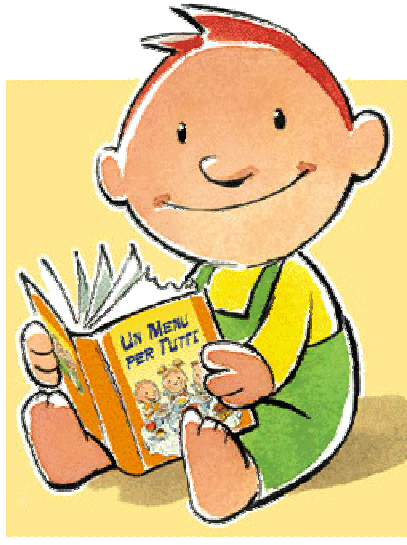


Language, Communication, and Literacy: Pathologies and Treatments

June 2007
Volume 54
Number 3

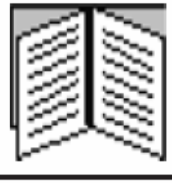
GUEST EDITORS
Robert L. Russell, PhD
Mark D. Simms, MD, MPH

Linguaggio e dislessia

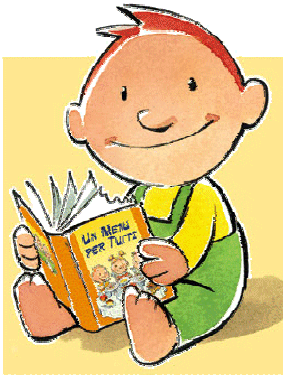


- La Dislessia non è un disturbo linguistico *per sé*
- La lettura non si sviluppa in modo spontaneo, universalmente e naturalmente, ma richiede un insegnamento specifico.
- Tuttavia, la maggior parte dei dislessici mostra deficit nella elaborazione linguistica, in particolare nella manipolazione dei fonemi.

Table 1 Terminology used to describe units of written and spoken language

Item	Examples						
Pictures							
Words	Book			Scarf			
Graphemes	B	OO	K	S	C	AR	F
Phonemes	/b/	/oo/	/k/	/s/	/k/	/ahr/	/f/

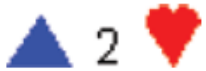
Rapporti tra linguaggio e lettura



- Il linguaggio contribuisce allo sviluppo delle abilità di lettura a diversi livelli.
- Lo sviluppo del linguaggio parlato ha un ruolo determinante nell'apprendimento della lettura.
- In particolare vi è una relazione forte tra le abilità del linguaggio parlato (incluso il vocabolario) e la comprensione del testo scritto.
- La padronanza del vocabolario gioca anche un ruolo nella acquisizione delle abilità di decodifica e di consapevolezza fonologica

(Grizzle KL Pediatr Clin N Am 2007;54:507-523)

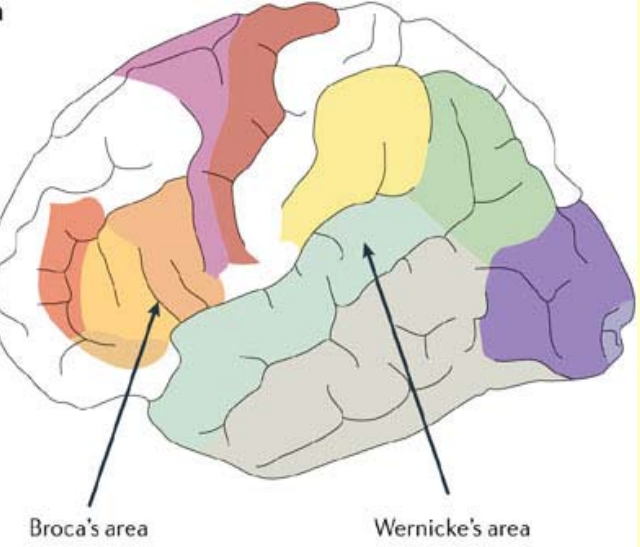
able 2 Reading-related measures to dissect cognition of reading

leasures	Description	Example
ngle-word reading	Individuals are asked to read aloud unrelated words of increasing difficulty until some error threshold is reached. This is the most commonly used test to diagnose dyslexia.	Cat Chair Mushroom Television Dictionary Laboratory
pelling	Test the ability to spell real words of increasing difficulty and various types. This test is also used to diagnose dyslexia.	
honological decoding	Ability to convert printed letter strings into speech sounds according to specific phonetic rules. Usually tests involve the reading of pseudowords.	Siglop Dorkit Pamdin
rthographic coding	Test the ability to recognize a word as a unit without fragmenting it. It is usually tested by reading irregular words that cannot be decoded by phonetic rules alone.	Yacht Salmon
	In the "forced choice" test individuals are asked to identify real words from pseudowords that would produce the same sounds.	Rain or rane? Fite or fight?
omonym choice	Similar to the forced choice orthographic coding test, except that the two test words are both real words pronounced the same but with different meanings.	Seven days constitutes a: Week or weak?
honological wareness	Ability to recognize and manipulate the smallest components of words, the phonemes. Individuals are usually asked to move phonemes around within the same word or swap them between words. Also known as "spoonerism."	spoon & dog  doon & spog
apid automatic aming	Ability to rapidly retrieve the names of visually presented stimuli (numbers, colors, objects). This skill is associated with reading fluency and is related to language ability.	

The eloquent ape: genes, brains and the evolution of language

Simon E. Fisher and Gary F. Marcus‡*

Abstract | The human capacity to acquire complex language seems to be without parallel in the natural world. The origins of this remarkable trait have long resisted adequate explanation, but advances in fields that range from molecular genetics to cognitive neuroscience offer new promise. Here we synthesize recent developments in linguistics, psychology and neuroimaging with progress in comparative genomics, gene-expression profiling and studies of developmental disorders. We argue that language should be viewe not as a wholesale innovation, but as a complex reconfiguration of ancestral systems that have been adapted in evolutionarily novel ways.



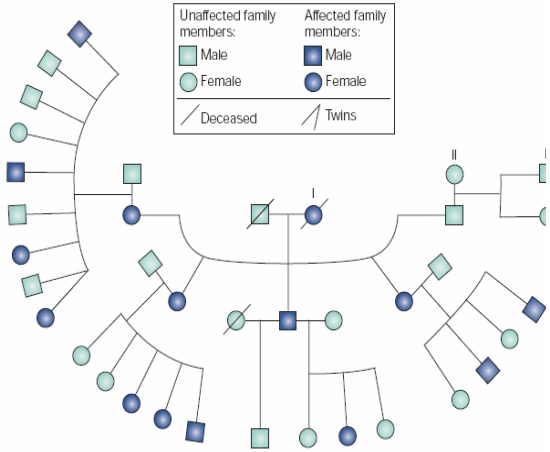
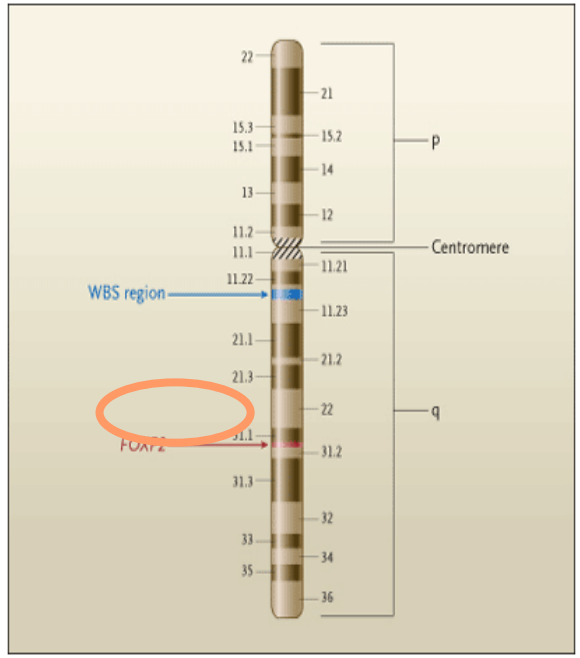
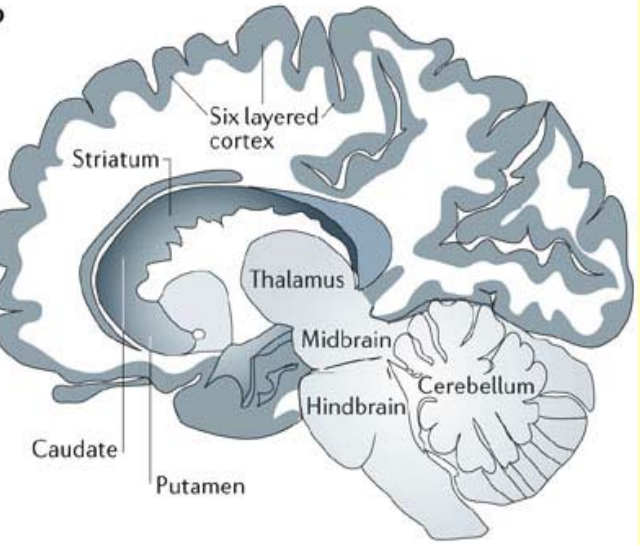


Figure 1 | **Pedigree of the KE family.** I, II and III represent the generations. Modified, with permission, from REF. 14 © (2002) Oxford University Press.

FOXP2

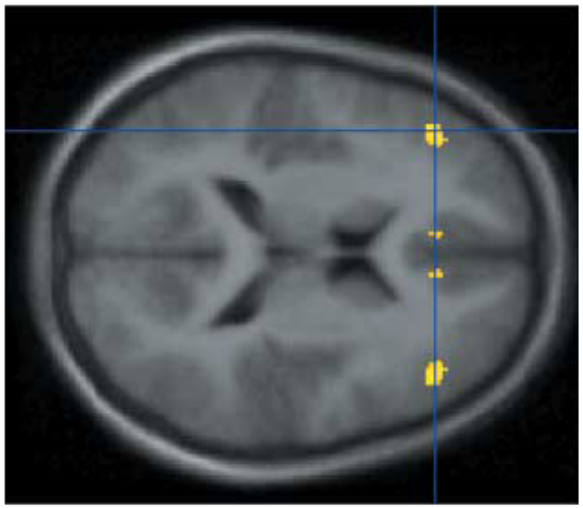




Nature Reviews | Genetics

Chromosome 7 Gene Dosage and Speech and Language Disorder.

Inferior frontal gyrus $p<0.0001$

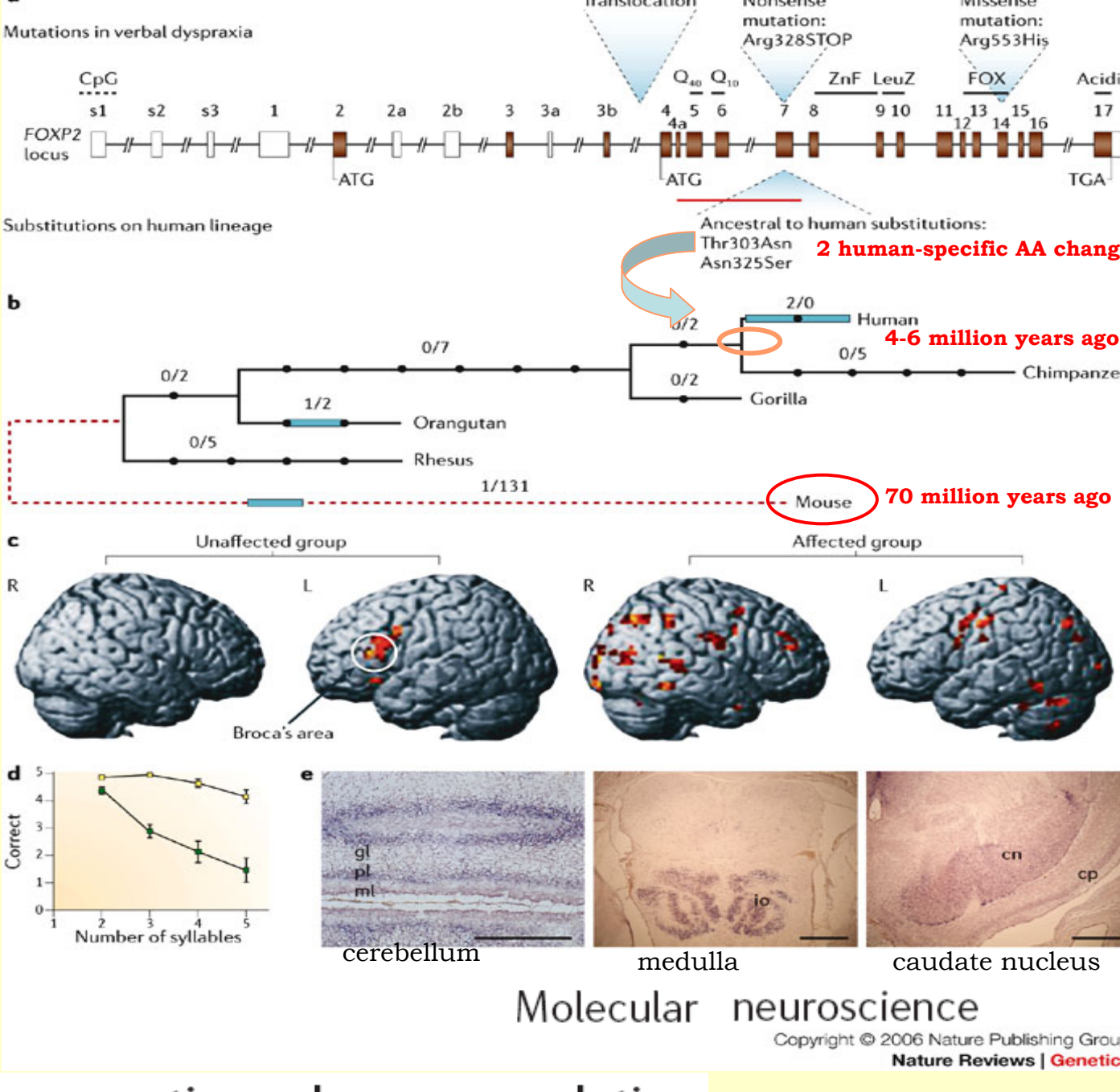


Genetics

Evolution

Neuroimaging

Neuropsychology



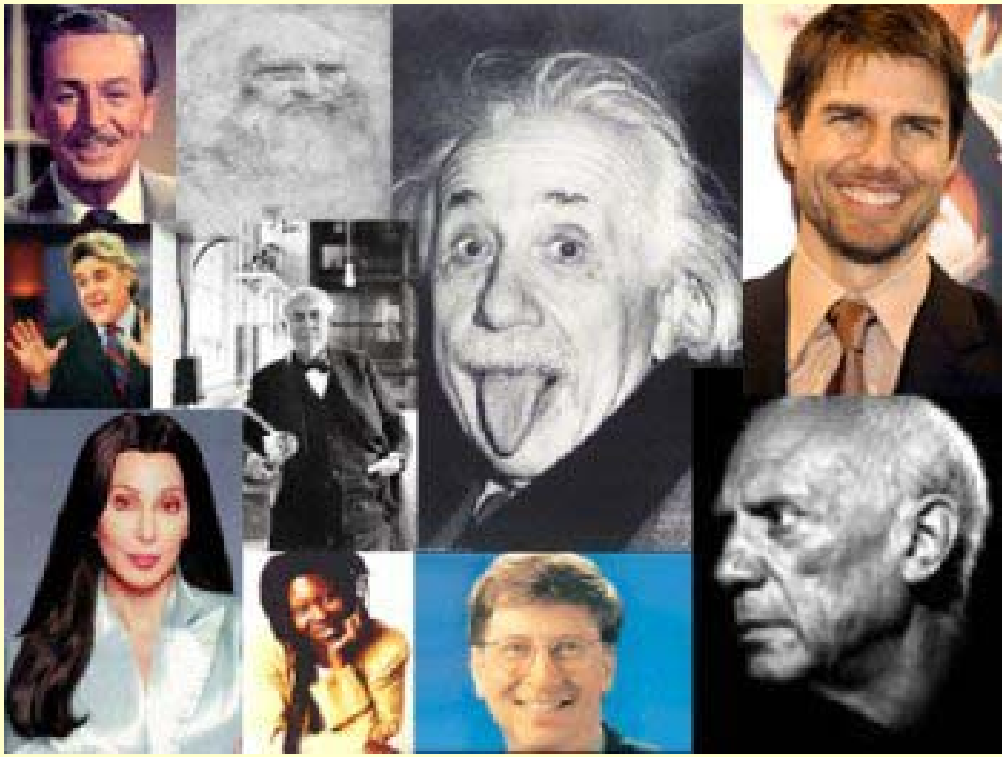
Molecular neuroscience

Historical Roots

Dyslexia has been described in virtually every ethnic group, language, and geographic region. The original report, published as *A Case of Congenital Wordblindness* on November 7, 1896, was prompted by the experience of a British physician, W. Pringle Morgan, with his patient Percy F., age 14, for whom he provided the following description:

> . . . He has always been a bright and intelligent boy, quick at games, and in no way inferior to others his age. His great difficulty has been—and is now—his inability to read. He has been at school or under tutors since he was 7 years old, and the greatest efforts have been made to teach him to read, but, in spite of this laborious and persistent training, he can only with difficulty spell out words of one syllable . . . .
>
> . . . I might add that the boy is bright and of average intelligence in conversation. His eyes are normal . . . and his eyesight is good. The schoolmaster who has taught him for some years says that he would be the smartest lad in the school if the instruction were entirely in oral . . . (Morgan 1896, p. 1378).

Core definitional concept: an unexpected difficulty in reading.



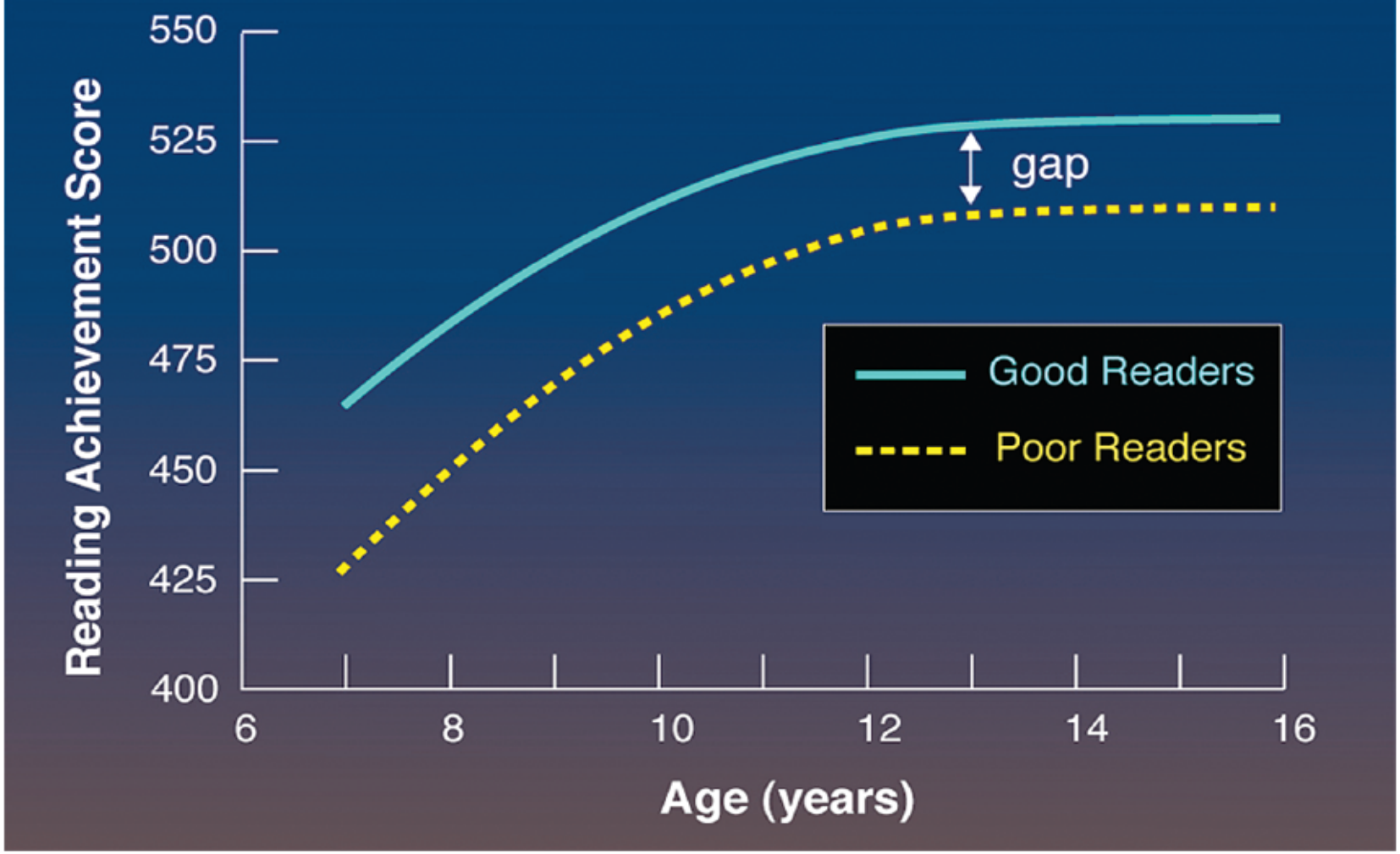


Figure 1

Trajectory of reading skills over time in nonimpaired and dyslexic readers. Ordinate is Rasch scores (W scores) from the Woodcock-Johnson reading test (Woodcock & Johnson 1989) and abscissa is age in years. Both dyslexic and nonimpaired readers improve their reading scores as they get older, but the gap between the dyslexic and nonimpaired readers remains. Thus, dyslexia is a deficit and not a developmental lag. (Figure derived from data in Francis et al. 1996 and reprinted from Shaywitz 2003 with permission.)

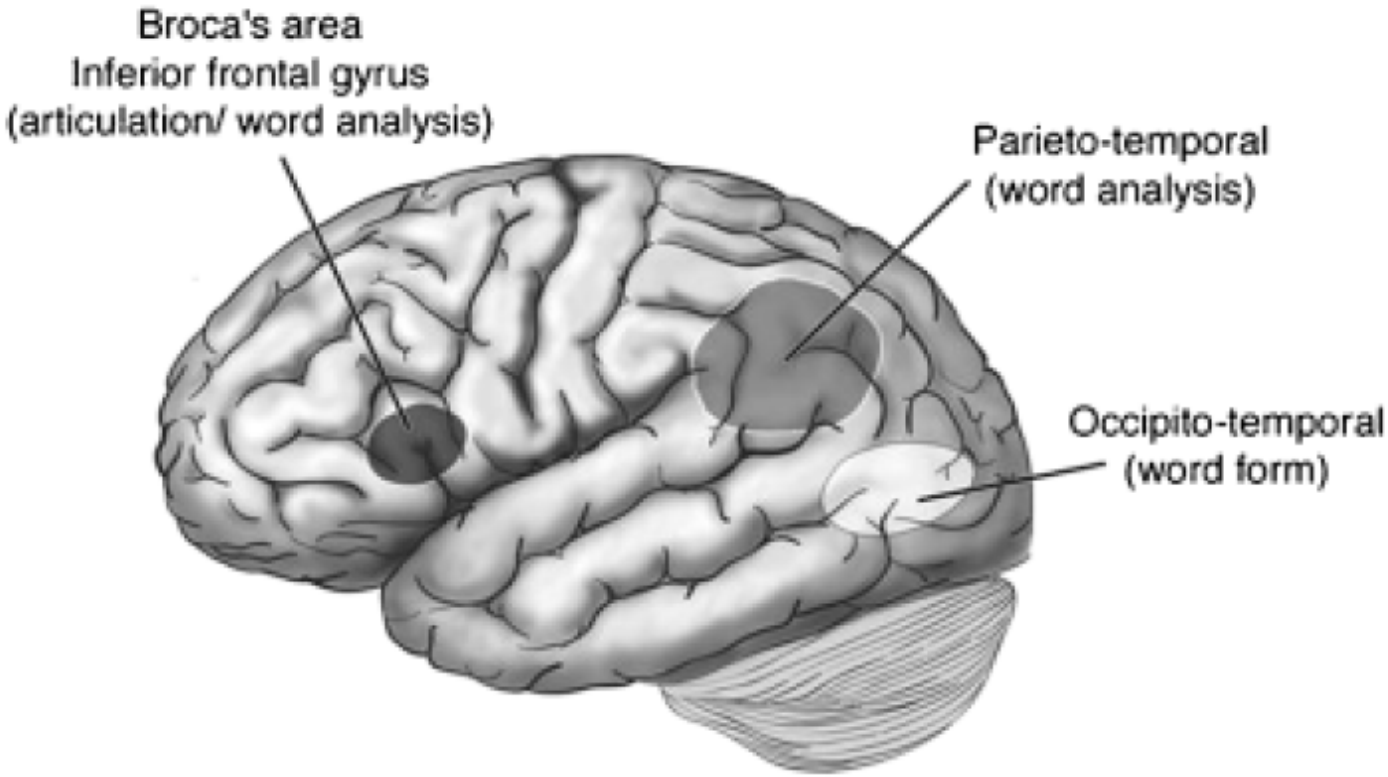


Fig. 1. Neural systems for reading in the brain's left hemisphere. An anterior system in the region of the inferior frontal gyrus (Broca's area) is believed to serve articulation and word analysis. A system in the parieto-temporal region is believed to serve word analysis, and a second in the occipito-temporal region (termed the word-form area) is believed to be responsible for the rapid, automatic, fluent identification of words. Reprinted from *Overcoming Dyslexia: A New and Complete Science-Based Program for Reading Problems at Any Level*, by Sally E. Shaywitz, 2003, p. 78, New York: Alfred A. Knopf. Copyright 2003 by Alfred A. Knopf. Reprinted with permission.

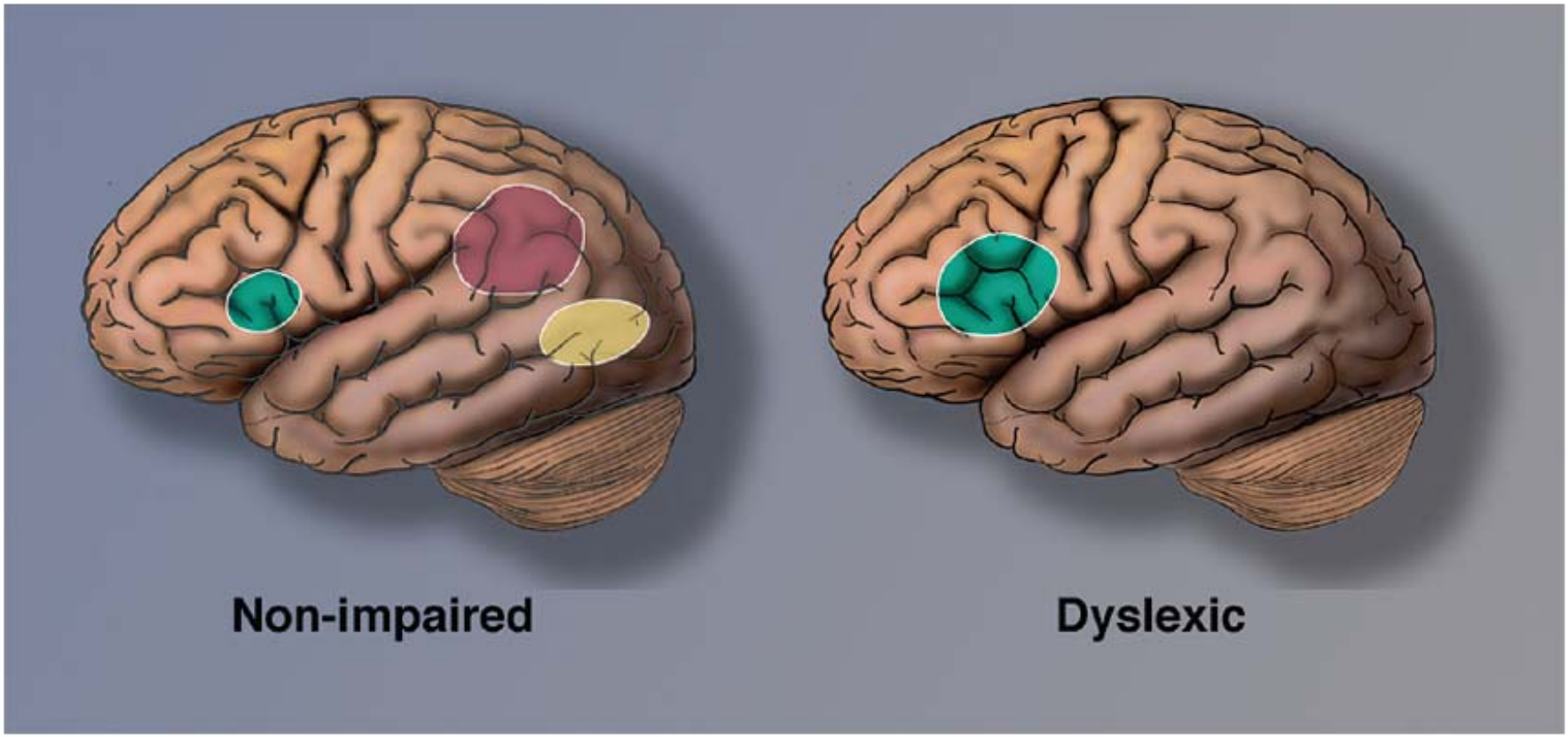


Figure 2

Neural signature for dyslexia. Schematic view of left hemisphere brain systems for reading observed during fMRI in nonimpaired (*left*) and dyslexic (*right*) readers. In nonimpaired readers, three systems are evident: one anterior in the area of the inferior frontal gyrus and two posterior, the top system around the parieto-temporal region and the bottom system around the occipito-temporal region. In dyslexic readers, the anterior system is slightly overactivated compared with systems of nonimpaired readers; in contrast, the two posterior systems are underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. Figure reprinted from (Shaywitz 2003) with permission.

THE GENETIC COMPONENTS OF DYSLEXIA

RD is familial and heritable, with family history being one of the most important risk factors (23, 75). The incidence of RD among siblings of affected individuals has been consistently reported to be approximately 40% (31, 44, 75, 102). Familial clustering is a good indication that genetic factors are involved in the etiology of the disorder but may also indicate the effect of shared environmental factors. Twin studies have been crucial to differentiate the relative contribution of genetics and environment. A large study of twins affected by RD has shown that the concordance rate in monozygotic twins, who carry the same genetic background, was 68% compared to 38% in dizygotic twins, who are genetically no more similar than nontwin siblings (20). These values suggest that genetic factors contribute significantly to RD, but cannot completely explain the causes of this disorder, which is likely the result of multiple genetic and environmental interactions.

Transmission of RD in family studies (74) and regression analysis of twin data (22) not only confirms the high heritability of RD but also shows that it is a genetically heterogeneous condition that usually is not inherited as a Mendelian trait. Linkage studies confirm this heterogeneity, identifying several genomic regions that may carry susceptibility quantitative trait loci (QTLs) for RD (33). Despite the use of different approaches, including differing proband ascertainment criteria, family structures, genotyping technologies, analysis software and algorithms, and phenotypic measurements, there is a

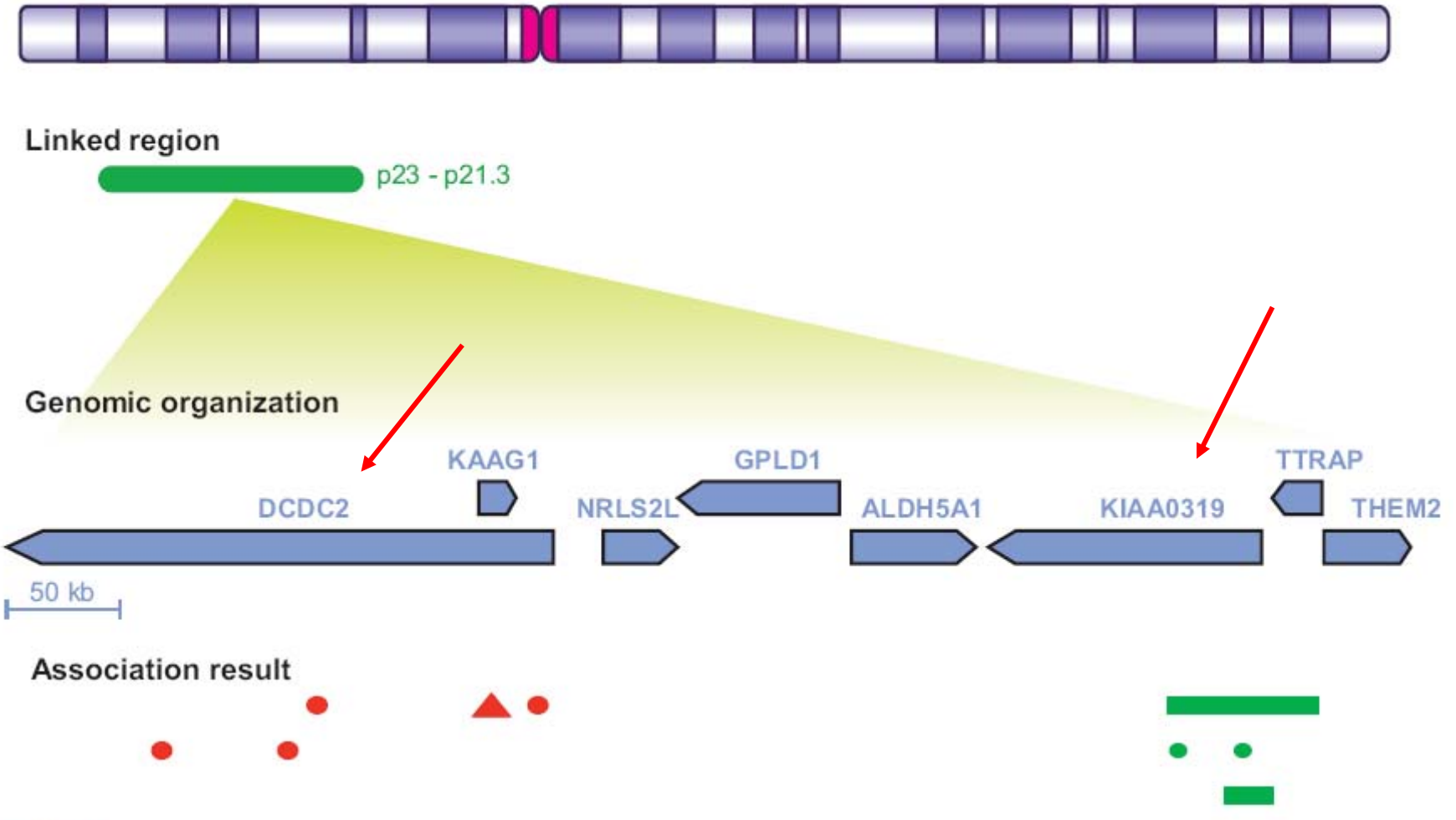
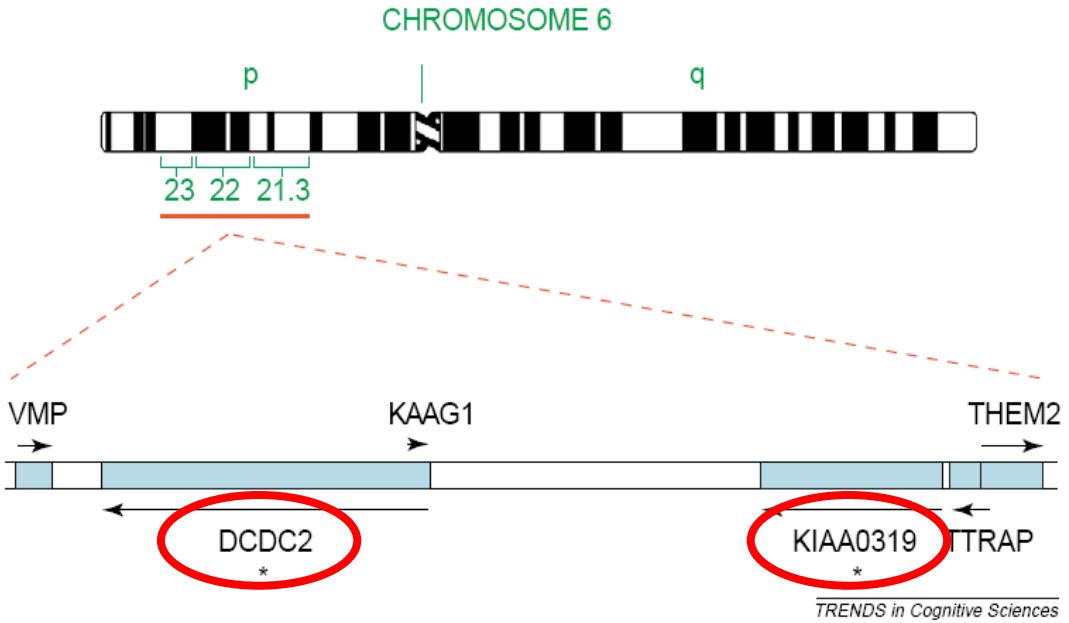
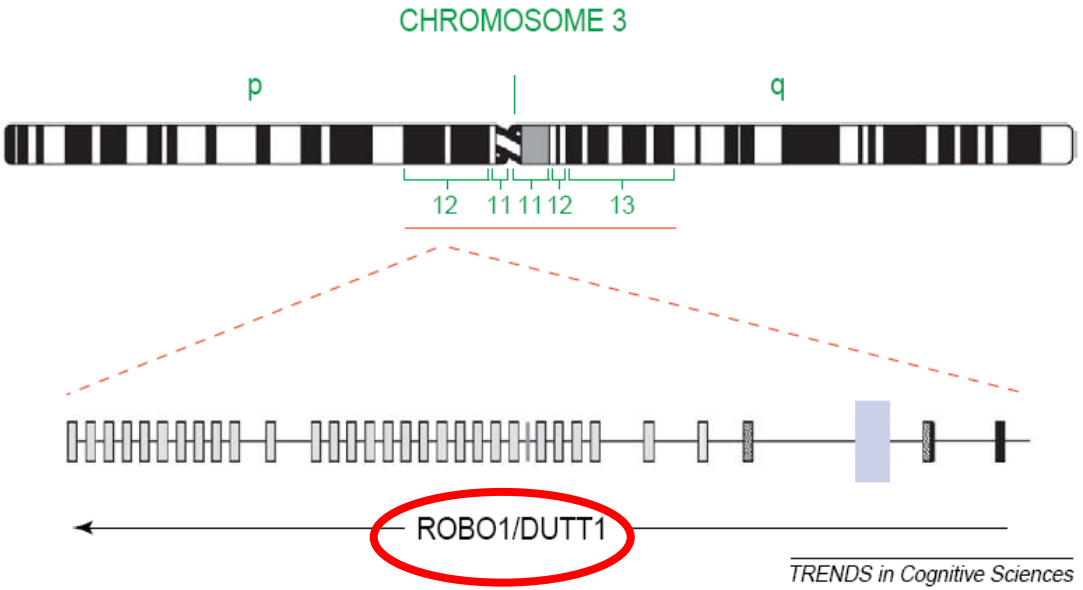
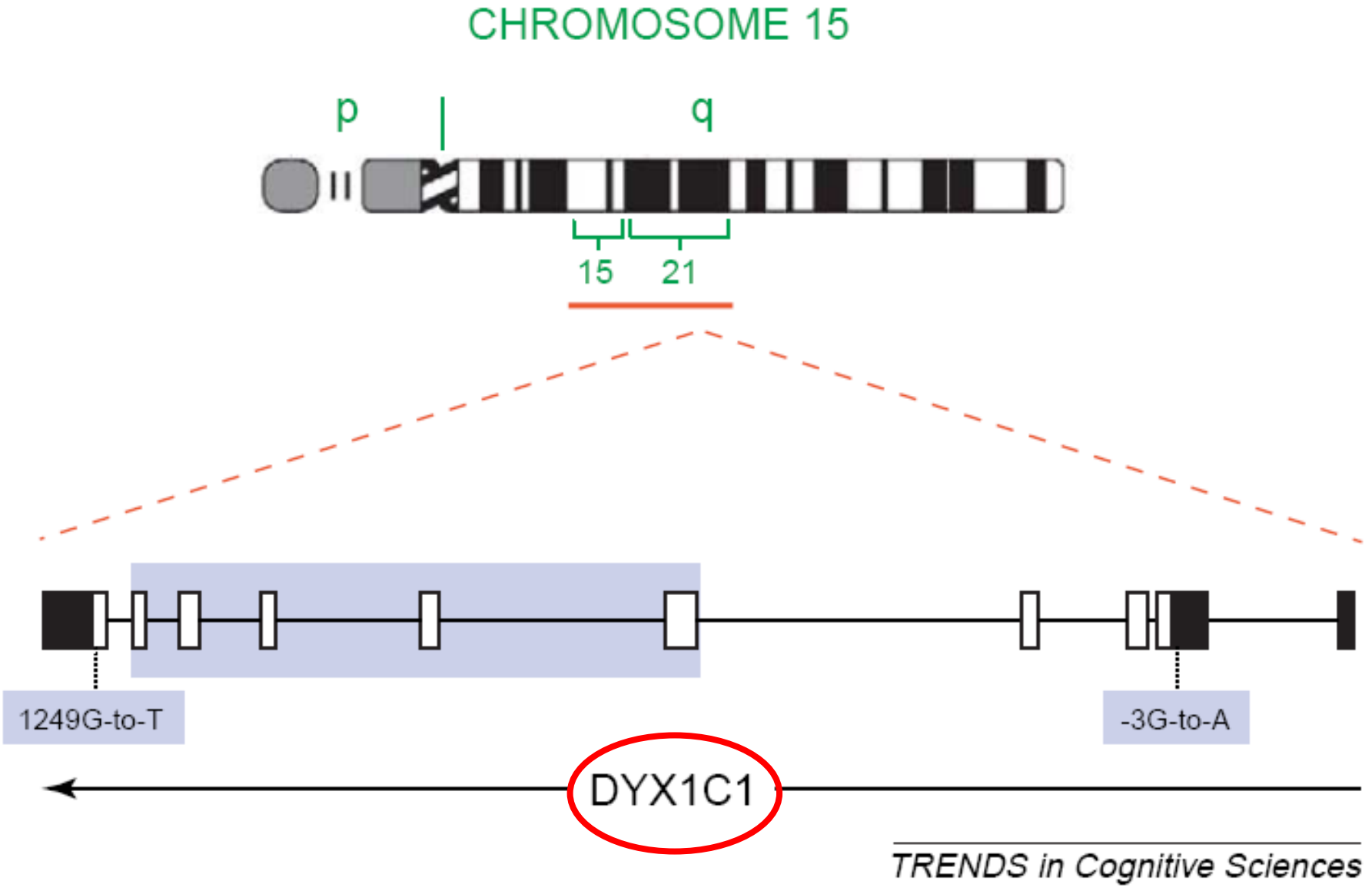


Figure 2

Results of association studies at the chromosome 6 locus. Linkage studies have identified a consensus region at chromosome 6p23-21.3 that has been implicated in harboring reading disability (RD) susceptibility variants. Association studies have detected positive signals within the *DCDC2* and *KIAA0319* genes, which are located within 200 kb of each other. The dots, triangle, and bars represent the SNPs, deletion, and genomic region, respectively, that produced the most significant association with RD. The markers from the studies of Meng et al. (66) and Schumacher et al. (83) are shown in red, and the markers from the studies of Francks et al. (39), Cope et al. (16), and Harold et al. (51) are in green.


CHROMOSOME 6
p
q
23 22 21.3
VMP
KAAG1
THEM2
DCDC2
*
KIAA0319
TTRAP
*
TRENDS in Cognitive Sciences


CHROMOSOME 3
p
q
12 11 11 12 13
ROBO1/DUTT1
TRENDS in Cognitive Sciences



The First Candidate Gene

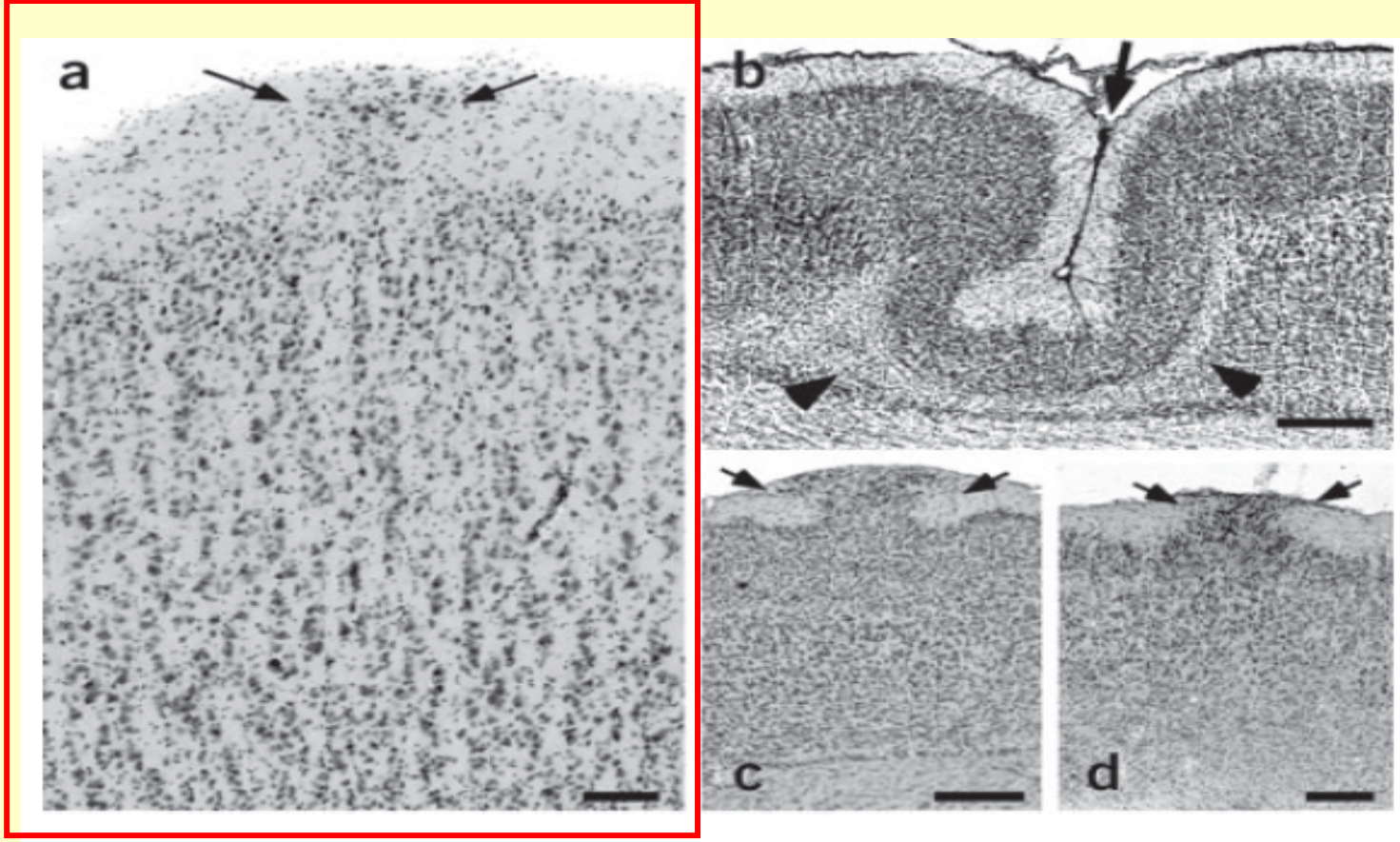


Figure 2 Human and animal neocortical malformations. (**a**) Molecular layer ectopia (arrows) in neocortical layer I of a human dyslexic. Scale bar, 100 μm. (**b**) Induced microgyria in a rat. This malformation, induced by placing a freezing probe onto the skull of a newborn rat, is generally characterized 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.

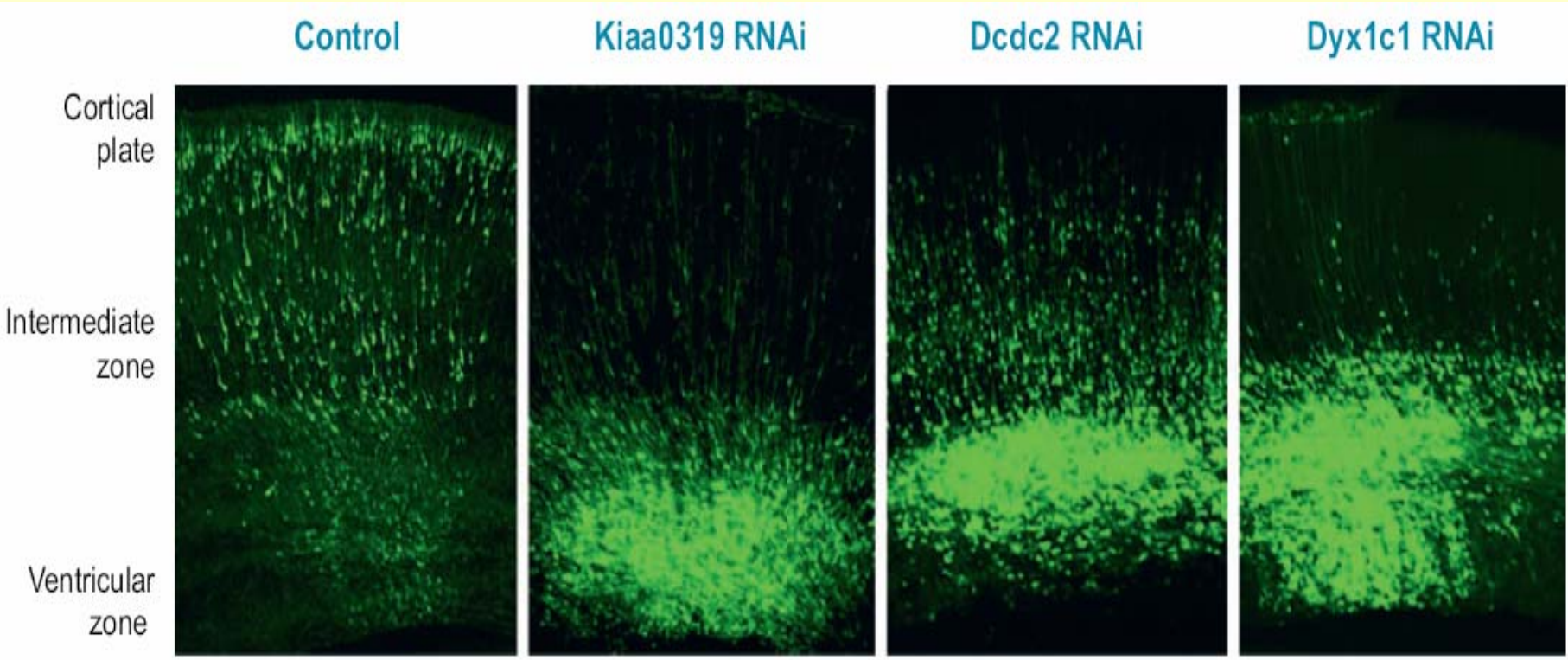


Figure 3

RNA interference (RNAi) of *Kiaa0319*, *Dcdc2*, and *Dyx1c1* disrupts migration in the developing rat neocortex. Images of sections of embryonic rat neocortex are shown four days after the electroporation of short hairpin RNA (shRNA) vectors and an EGFP vector, as described by Bai et al. (3). In the control experiment, where cells were transfected with a neutral shRNA, most of the neurons migrated well away from the ventricular zone and many reach the cortical plate. Neurons transfected with shRNA vectors against *Kiaa0319*, *Dcdc2*, and *Dyx1c1* migrate abnormally and are arrested in the ventricular and intermediate zones. Credit: Joe LoTurco, University of Connecticut.

NEURONAL MIGRATION: THE PATH FROM GENES TO COGNITION

The candidate genes discussed so far have been proposed on the basis of genetic mapping approaches and statistical analysis. But how can these genes be relevant to the development of RD? In other words, what do these genes do? The answer will not only be the key to understanding the biological mechanism leading to dyslexia, but it will also provide essential tools to penetrate the labyrinth of cognition (34). There is evidence that all four candidates are required during the development of the brain, and they all seem to take part in pathways involved in axon growth and neuronal migration (41).

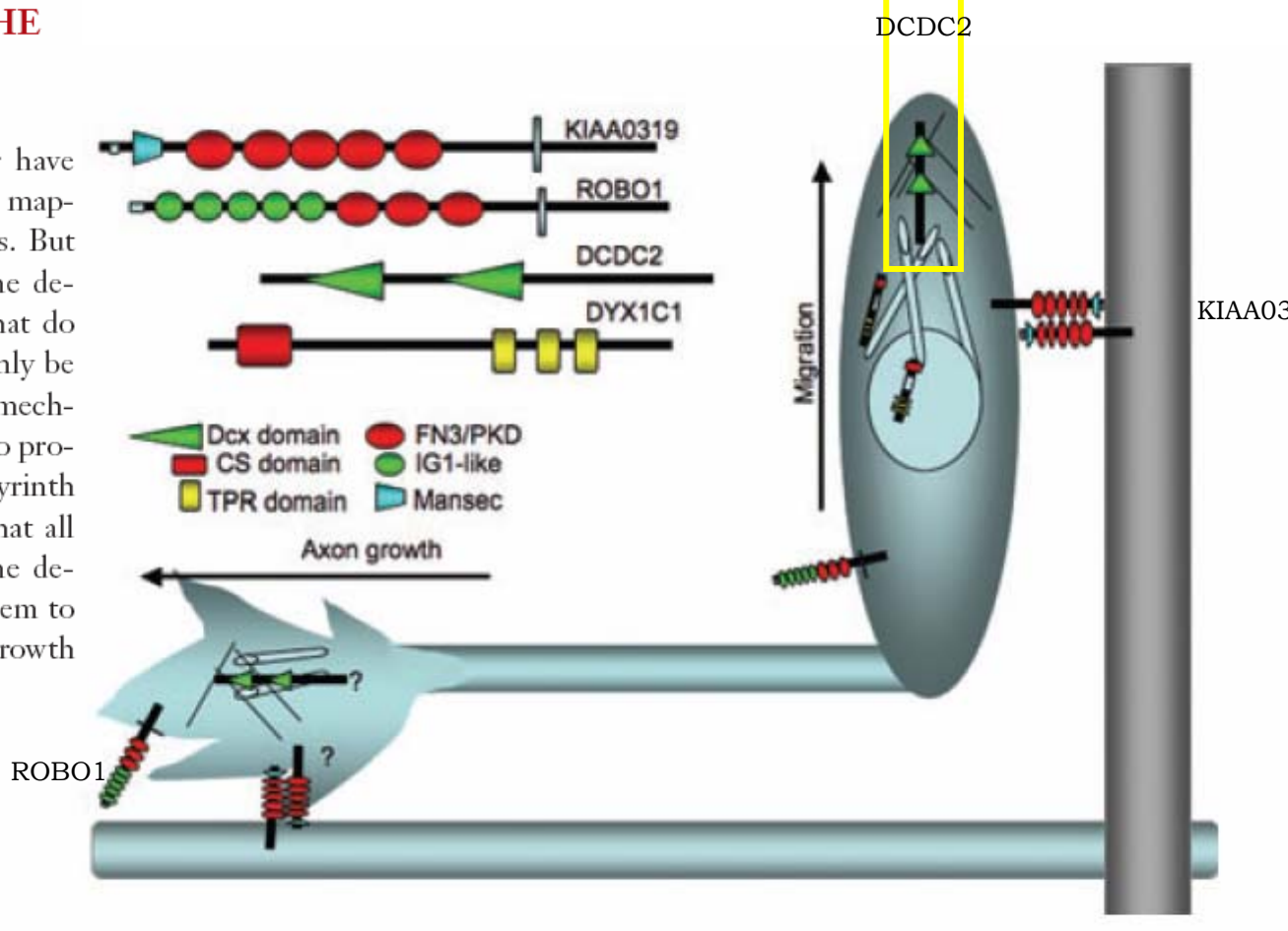
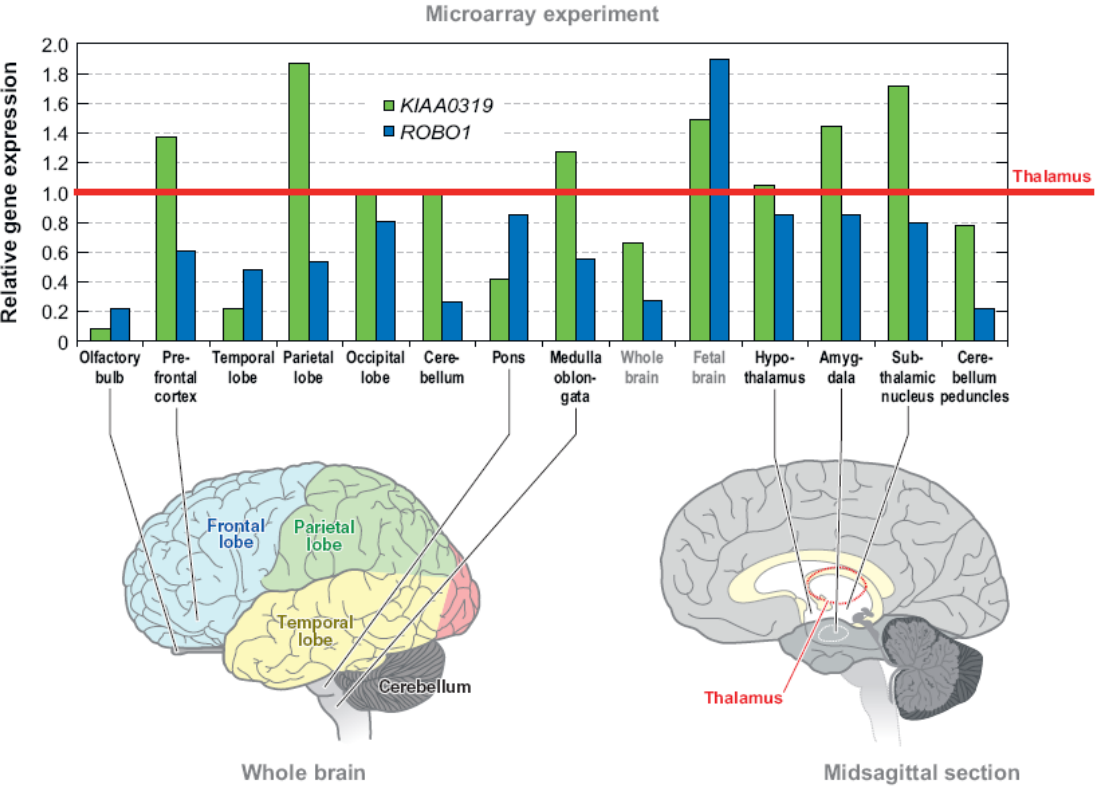


Figure 1 Protein domains and possible functions. KIAA0319 and ROBO1 serve as transmembrane adhesion molecules and receptors that guide axons to appropriate targets. DCDC2, and perhaps DYX1C1, are proposed to act as downstream targets that then serve to modulate changes in cytoskeletal dynamic processes 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.



As we previously discussed, a reduced gene expression was also associated with the risk haplotype for the *ROBO1* gene (50). Even if those findings are still waiting further replication, they support the idea that altered regulation of gene expression could be a common theme for genes involved in dyslexia.

RD is a complex trait, expected to be the result of the concomitant effect of multiple genetic and environmental factors. Each of these factors is anticipated to contribute a small effect to the overall trait, thus creating a continuum of abilities within the general population. A susceptibility genetic variant will be relevant to a dysfunction depending on the epistatic architecture of the genome. A subtle factor such as variation in the level of a specific protein, if combined with other elements could be enough to play a role in the development of a complex trait (57). It has already been shown that allelic variation influencing gene expression is a common feature of the human genome (60, 109), and this variation could contribute significantly to human variability. Therefore, finding that a specific allele associated with RD is also regulating the expression of a specific gene supports this model

Alcune conclusioni…

La lettura è un'abilità complessa

I geni codificano per elementi costitutivi che rendono possibili i processi neuropsicologici più elementari coinvolti nel processo di lettura

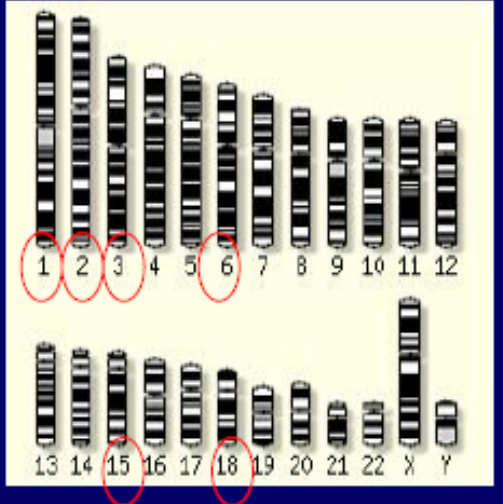
Più geni sono coinvolti nel determinare la suscettibilità a sviluppare la dislessia

Conosciamo la localizzazione di alcuni geni, ma non la loro funzione

Ognuno di questi geni non è necessario e non è sufficiente

La difficoltà di lettura è mediata dall'azione congiunta di almeno due o più di questi geni

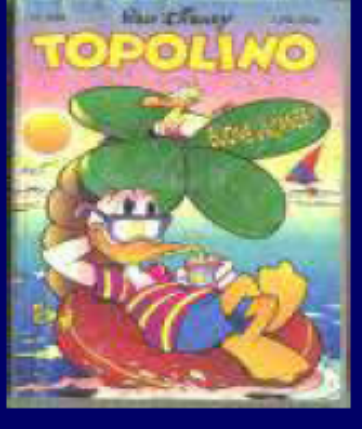
Ogni gene ha un effetto, più o meno determinante sulla manifestazione della dislessia



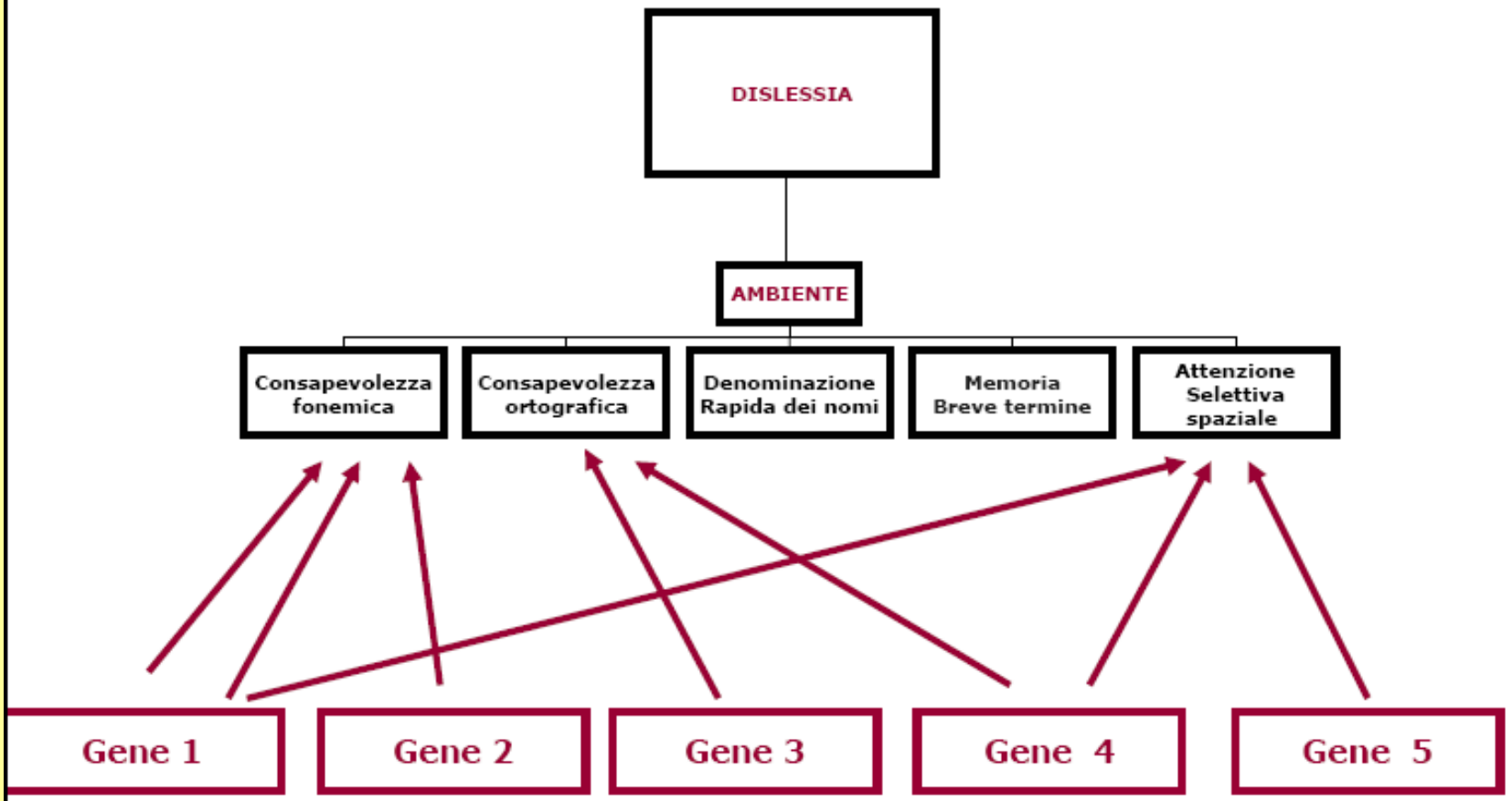
Non sempre possedere tutti i geni necessari e sufficienti determina la manifestazione della difficoltà di lettura

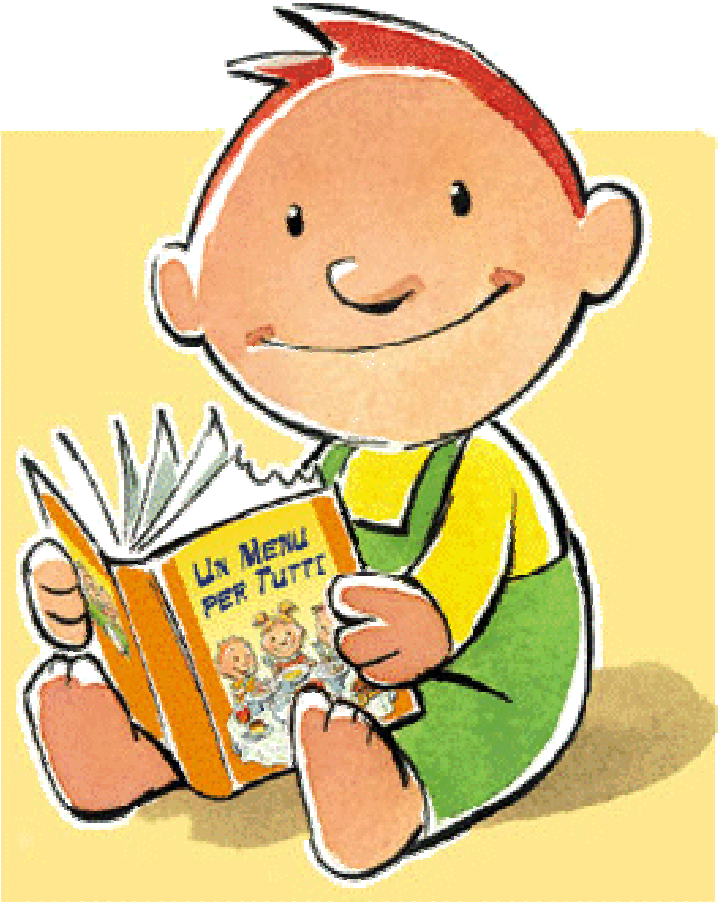
- **Un ambiente sfavorevole può contribuire alla manifestazione del puzzle genetico pro dislessia**

- **Un ambiente favorevole può nascondere il puzzle genetico pro dislessia**



Un modello di trasmissione complesso





Grazie dell'attenzione!