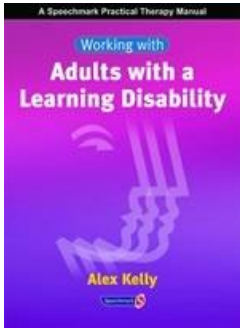
Psych 3102
Introduction to Behavior Genetics

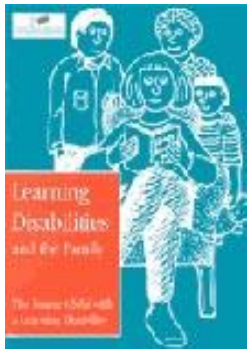
Lecture 17

Genetics of cognitive disabilities

Learning disorders

Learning disorders





Diagnostic criteria

- achievement below expected for age, schooling, general cognitive ability
- significantly interferes with achievement in life

Prevalence: 2-10% in general population
5% in public schools

Types: written expressive disorder no genetic studies
mathematics disorder moderate genetic influence
+ overlap with reading disorder
reading disorder 80% of all cases of learning disorders
60-80% of cases are males (bias in ascertainment?)

Reading disability (RD)

- scoring 1.5 sd below mean for single-word decoding test
- not explained by environmental deprivation, poor education

dyslexia specific reading disorder , phonological deficit, poor accuracy & speed of single-word recognition

Prevalence = 5 -17% av=8% for reading disabilities

- most studied learning disorder
- large population family studies show a genetic component h^2 = 44-75% av =70% (varies by sample and diagnostic criteria)
- low end of reading ability range?
- shared e generally less than 20%
- replicated studies have located QTLs

Colorado Adoption Project Reading disability study

Dick Olson, John DeFries

1044 individuals from 125 families containing a reading-disabled child + 125 matched control families

- sibs and parents in reading-disabled proband families scored poorly on reading tests compared to control family members
- could be genes or shared environment

Risk = 40% in siblings of affected

Prevalence = ~8%

Colorado Twin study Longitudinal study of reading disability

250 twin pairs where one or both twins were reading disabled

concordances: MZ = 66%

DZ = 36%

- resemblance found in family studies is at least partly due to genes as well as shared environment

Meta-analysis of RD studies

- 60% of mean difference between probands and population is heritable
- RD is the tail end of distribution for reading ability

ie NOT qualitatively different, SAME genes influence RD and normal range

- some 'risk' alleles for low ability likely DF extremes analysis

Word-reading deficit

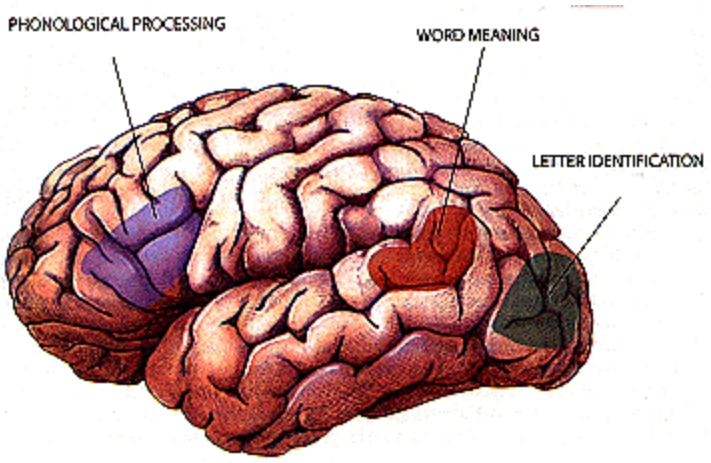
- a quantitatively-measured component of reading disability

Gayan & Olson (2002) Developmental Neurophysiology

h^2 = 54% + epistasis

- some specific alleles for disorder indicated by DF extremes analysis, but largely reading 'disorder' represents tail end of reading ability distribution

e^2 = 0.06% c^2 = 39% complex environmental influence



Locating genes for reading disability

Cardon et al (Science, 1994) + many replications since

QTL linkage analysis using the sibpair allele-sharing method

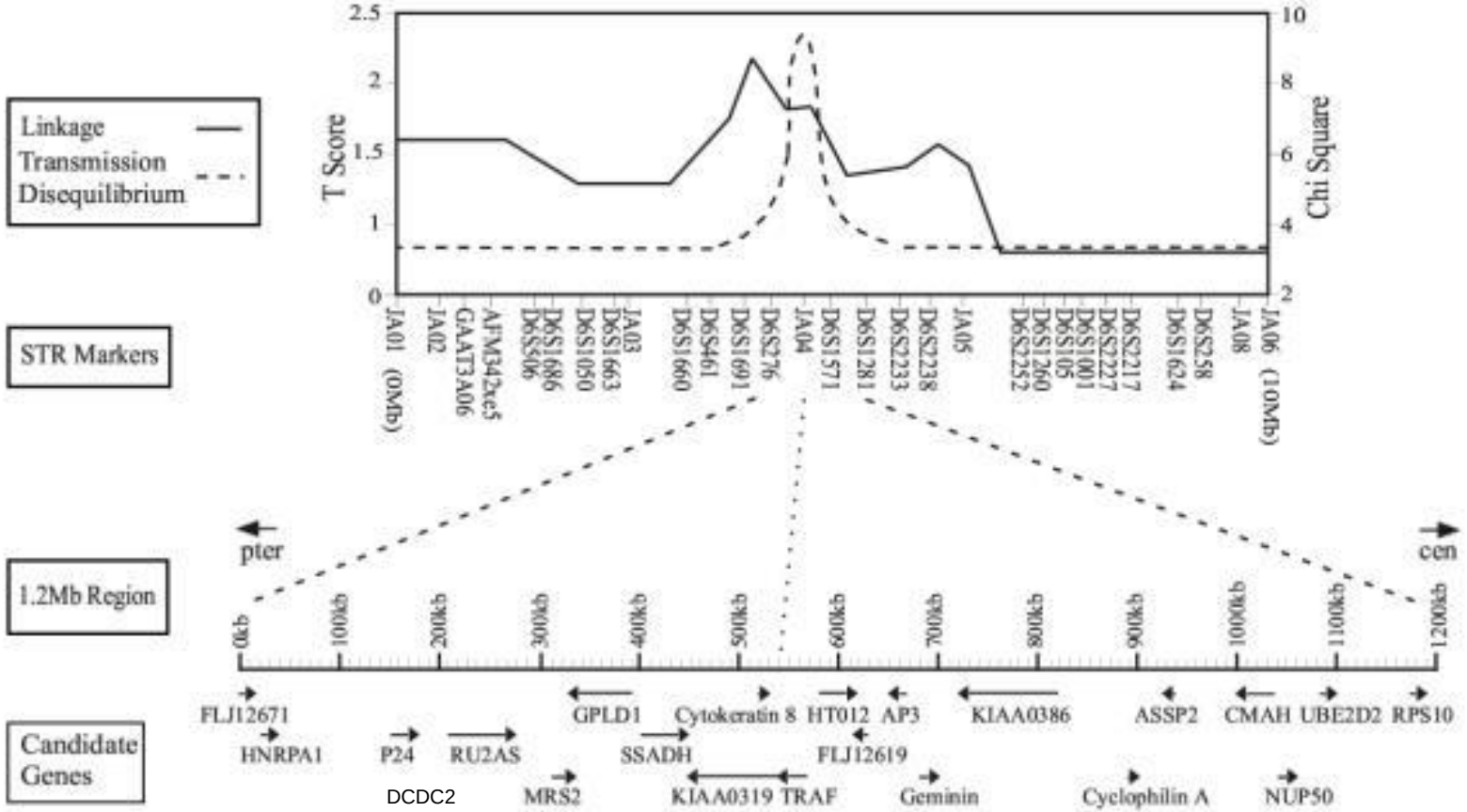
- locates QTLs for the trait by looking for allelic variation at marker loci that influences trait variation among sib pairs
- made more powerful by selecting probands with extreme scores for reading disability

Located markers linked with reading disability on chromosome 6p21

region of KIAA0319 gene

DCDC2 gene (patented)

- replicated in normal reading & spelling ability sample (Luciano et al, 2007, Biol Psyc 62)



Transmission disequilibrium and genetic linkage analyses of the 6p21.3 reading disability locus, regional STR markers and transcription map. At the top of the figure is the result of the DeFries-Fulker linkage (T Score, solid line), and QTDT linkage disequilibrium (chi-square, dashed line) [14]. The location and order of the 29 STRs are shown below which identify a peak of transmission disequilibrium at marker JA04. Below the markers is a detailed representation of 1.2 Mb surrounding marker JA04. The 19 genes and 2 pseudogenes encoded in this region are shown with the telomere on the left and centromere on the right and their position and direction of transcription indicated by the arrows.

Currently 9 regions of genome being investigated after previous studies & recent whole genome scan implicated them in variation for reading & spelling measures.

all loci given DYX# 1-9

DYX2 KIAA0319 transmembrane protein

DCDC2 double cortin domain containing gene 2

5 DCDC genes implicated (including Xq locus) - participate in brain development? (neural migration)

Galaburda et al, Nature Neuroscience, 2006

- abnormalities in brain development reported in dyslexia
- comparable abnormalities induced in animal models cause auditory, cognitive deficits
- brain abnormalities thought to lead to phonological & auditory processing abnormalities & mode of action of these genes is suggested

nature neuroscience

From genes to behavior in developmental dyslexia

Albert M Galaburda, Joseph LoTurco, Franck Ramus, R Holly Fitch & Glenn D Rosen

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 dyslexia[1]. Subtle cortical neuronal migration anomalies were observed in several post-mortem brains[2]. Findings consistent with congenital brain malformations were reported in a few cases of dyslexia and developmental language disorders. In one autopsy case[3], 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 heterotopia[4], and 13 children with perisylvian polymicrogyria (a form of abnormal neuronal migration) and developmental language deficits[5].

The most consistent findings in the original cases[2] 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 circumstances[15]. 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 sounds[16]. 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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