The genetic basis of dyslexia

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Dyslexia, a disorder of reading and spelling, is a heterogeneous neurological syndrome with a complex genetic and environmental aetiology. People with dyslexia differ in their individual profiles across a range of cognitive, physiological, and behavioural measures related to reading disability. Some or all of the subtypes of dyslexia might have partly or wholly distinct genetic causes. An understanding of the role of genetics in dyslexia could help to diagnose and treat susceptible children more effectively and rapidly than is currently possible and in ways that account for their individual disabilities. This knowledge will also give new insights into the neurobiology of reading and language cognition. Genetic linkage analysis has identified regions of the genome that might harbour inherited variants that cause reading disability. In particular, loci on chromosomes 6 and 18 have shown strong and replicable effects on reading abilities. These genomic regions contain tens or hundreds of candidate genes, and studies aimed at the identification of the specific causal genetic variants are underway.

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Dyslexia (previously called congenital word blindness) is a specific impairment in reading ability that cannot be explained by deficits in intelligence, learning opportunity, motivation, or any overt neurological handicap.[1,2] Roughly 5% of schoolchildren are affected by dyslexia. Many adults with dyslexia can attain normal standards of reading, but the disorder remains apparent through poor reading fluency.[3] The first case of congenital word blindness was diagnosed over 100 years ago,[4] but despite intensive research the molecular and developmental aetiology of the disorder has remained unclear. However, the observation that dyslexia tends to run in families was made early on,[5] and more recently, twin studies have confirmed that genetic factors underlie a large proportion (30–70%) of population variability in reading measures.[6–12]

Written language is the basis of education systems throughout the world, and failure to benefit from educational opportunities can be a severe handicap with lifelong socioeconomic and mental-health consequences.[1] There is a need for the molecular pathogenesis of dyslexia to be understood, in the expectation that knowledge of the underlying biology will enable more rapid diagnosis and better targeted remedies.

Biology of reading

Reading is a complex multicomponent process both physiologically[2] and cognitively.[8,12] In brief outline, reading must begin with sensing of visual stimuli and processing of information through the pathway of retina, lateral geniculate nuclei, and primary visual cortex.[13] At some stage, visual information is probably made available to neuronal systems that apply learned, language-specific rules to convert symbolic images into component representations of language.[14] In this form, the information may flow into normal language processing systems that exist in the brain whether or not a person has learned to read,[15] and that perhaps evolved for processing of spoken language. Reading-related cognition is accompanied by high activation of left-hemisphere cortical regions, including some known to be important in language processing.[16–18] However, learning to read may also depend on other implicit learning processes, perhaps mediated partly by the cerebellum,[19,20] and on feedback between these systems. A simple example of feedback is that eye movements during reading must be appropriately regulated by previous progress along a line of text or through a word; hence, fine sensorimotor coordination must also be involved.[21,22]

Correlated deficits

A deficit in reading ability might stem from diverse disruptions to the range of neural systems used in reading, from simple sensory impairments to impairments in complex cognitive processes, particularly those related to language. Researchers have used psychophysical, event-related potential, and functional brain-imaging methods to study differences between individuals with dyslexia and controls during a wide variety of sensory,[2,17,23–26] cognitive,[27–31] and behavioural[19,20] tasks. Sensory correlates of dyslexia include difficulties with the processing of visual and auditory stimuli at high temporal resolutions. Cognitive deficits can be found in component-reading and language-related skills.[8] Finally, behavioural correlates of poor reading include impaired motor and balance coordination[19,20] and attentional deficits.[32] Whether some or all of these correlated symptoms cause reading difficulties, as opposed to being comorbid signs of an underlying neurological disorder, is unclear. However, characteristic profiles of deficits across these kinds of measures could eventually be used to identify and diagnose aetiological subtypes of dyslexia.

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Glossary

Phonological awareness
Ability to reflect explicitly on, and manipulate, the units of spoken language.

Phonological decoding
Parsing written text into phonetic units, usually measured by reading of nonsense words (eg, tegwop).

Orthographic coding
Reading words by recognising their holistic form, usually measured by reading irregular words that violate standard letter-sound conventions (eg, yacht).

Word recognition or single-word reading
Reading of single real words of various types and difficulties as an indicator of overall reading ability.

Rapid automatic naming
Speed of calling the names of simple visually presented stimuli after presentation, eg, colours.

Spelling
Ability to spell real words of various types and difficulties correctly.

Cognitive aspects of reading

Researchers typically attempt to dissect the cognition of reading into conceptually distinct component skills. The close relation between reading and language lies at the heart of many efforts to identify cognitive deficits involved in dyslexia. In particular, the form in which deconstructed language is processed has provided the main focus for cognitive models of reading disability.27 In this regard, dyslexia research overlaps with research into specific language impairment (SLI), a closely related disorder. SLI refers to a failure to develop normal receptive or expressive language ability; like dyslexia, it is an aetiologically complex trait with a strong but heterogeneous genetic component.1,33 The clinical distinction between dyslexia and SLI belies a high comorbidity rate between the two disorders, which is difficult to quantify precisely given the phenotypic complexity of both. Deficits in the use of correct language syntax can be traced in young children with a familial risk of dyslexia before reading begins, and many people with dyslexia show delayed speech acquisition and increased rates of speech errors, such as lisps and spoonerisms.1,33

Most genetic studies of dyslexia now use a battery of tests aimed at measuring a range of reading-related cognitive skills,[8,34–40] such as phonological awareness, phonological decoding, orthographic coding, word recognition, rapid automatic naming, and spelling. Correlations between these measures are typically highly significant (in the range of 0·3–0·8 in samples of reading-disabled and normal children),[8,12,38] although individuals with dyslexia can differ widely in their particular profiles of deficits and abilities across the range of reading-related measures.[8,14,38]

Phonological awareness

All words in the English language are constructed from combinations of 44 unique speech sounds called phonemes.[41] For example, the word "cat" is constructed from the phonemes /kuh/, /aah/, and /tuh/. Phonological awareness refers to the ability to be explicitly aware of and to manipulate these segments of speech.[8] Many people with dyslexia often do poorly on such tests throughout their lives, even when their overall reading has improved.[1,3] Tests of phonological awareness are presented aurally and responded to orally. The tasks may include moving specific phonemes around within words, or swapping phonemes between words (eg, take the first phoneme from "dull" and swap it for the first phoneme of "log", for which the correct answer is "dog").[38] A deficit in this ability is thought to impede the normal learning of sound–symbol relations that are used to decode printed words.[8]

Phonological decoding

This term refers to the ability to parse a printed word or nonsense word (eg, baim, dysical) into relevant phonetic units and translate them into a string of speech sounds in order to pronounce words according to a single set of language-specific rules.[8,14] A phonological decoding strategy allows individuals to tackle new and unfamiliar words and may be particularly important in early reading.[14] Most tests involve the reading of printed nonsense words aloud. Again, these tests often reveal lifelong deficits in individuals with dyslexia.

Orthographic coding

The orthographic pattern of a word refers to its unitary and holistic appearance when printed, and orthographic coding refers to the hypothetical process of recognising a word by its holistic form without subdividing it.[8,14] This ability is normally assessed by asking individuals to read aloud irregular words—which violate standard letter–sound conventions so that a phonological strategy will not work (eg, yacht or brooch)—or to make forced choices between visually presented real words and phonologically similar background foils. Orthographic coding may be a more efficient mechanism for reading familiar words than phonological decoding, and therefore orthographic coding may take on an ever more important role as readers gain experience. Some individuals show more striking deficits on orthographic coding measures than they do on measures related to phonology.[14]

Word recognition or single-word reading

In tests of word recognition, individuals are shown unrelated words of increasing difficulty that they are asked to read aloud until some error criterion is reached. This method is commonly used to assess childhood "reading age" in schools in the UK, and, in many cases, dyslexia is diagnosed as a deficit in this ability.[1]

Rapid automatic naming

The ability to call rapidly the names of simple visually presented stimuli (eg, letters, digits, objects, colours) has been shown to relate to word recognition ability.[8,12,42] Rapid automatic naming may be an important part of successful reading outside of the group of processes relating more closely to language.

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Spelling

Spelling deficits are also commonly used to diagnose dyslexia in a clinical or educational setting.[1]

Development

In cognitive terms, single-word reading is sometimes described as a multicomponent process, intermediate in a nested hierarchy of processes that range from basic phoneme processing to the overall comprehension of extended text. As such, single-word-reading ability has been described as a broad and definitive indicator of reading skill,[34] with population variance in some of the other component skills thought to account for the overall variance within single-word-reading measures.[8]

However, hypothetical cognitive constructs such as phoneme awareness cannot be too readily equated with what is actually measured by the specific tests. Even the best designed reading-related test is likely to call on cognitive processes that have not been explicitly considered in the test design. Also, while the neurobiology underlying such processes remains largely unknown at a systems level, care must be exercised in attempts to construct notional hierarchical relations between these measures. In addition, some of the cognitive abilities described above do not fit neatly into a simple hierarchy even in theory (for example rapid automatic naming ability). Another important caveat is that the development of any reading-related process will probably affect others during childhood brain development. Finally, any specific modular cognitive model may not be equally applicable to adults and to young children.[43]

For these reasons, it may be sensible to abandon the idea of a cognitive hierarchy, and instead to investigate relations between all cognitive measures on an equal footing by use of multivariate quantitative analysis (eg, correlation, covariance, and factor analysis).[8,12,38] In addition, tests of reading-related abilities typically yield continuous and unimodal distributions in the general population; there is little compelling evidence for a second mode in the deficit range to suggest a wholly distinct dyslexic aetiology or a non-arbitrary diagnostic threshold.[1,38] Therefore, in genetic analyses of dyslexia, it can be helpful to discard the idea of the disorder as a categorical trait, or even as a set of categorical traits, and instead think in terms of the extremes of continuous variation.[8,38,44,45]

Genetic epidemiology

A genetic involvement in dyslexia has long been evident from studies showing familial clustering of the disorder[1,3,38] and more recently through twin studies.[6–9,12] In twin studies, monozygotic twins will be, on average, more similar for measures that are heritable than dizygotic twins, since monozygotic pairs share all of their segregating alleles identical-by-descent from their parents, as opposed to dizygotic twins who share, on average, half.[46] Environmental effects are assumed to be of equal importance for both types of twin pair. Probandwise concordance rates for dyslexia, estimated from the Colorado Twin Study of Reading Disability,[6,8,12,44,45,47] were 68% for monozygotic and 38% for dizygotic twin pairings. These estimates vary according to the diagnostic criteria used.[1] In quantitative terms, individual heritabilities for reading-related cognitive measures, again derived from twin studies,[6–9,12] normally range between 30% and 70%. That is to say 30–70% of the variability in such measures is genetically determined, at least within the lower tail of ability for these tasks (figure 1).

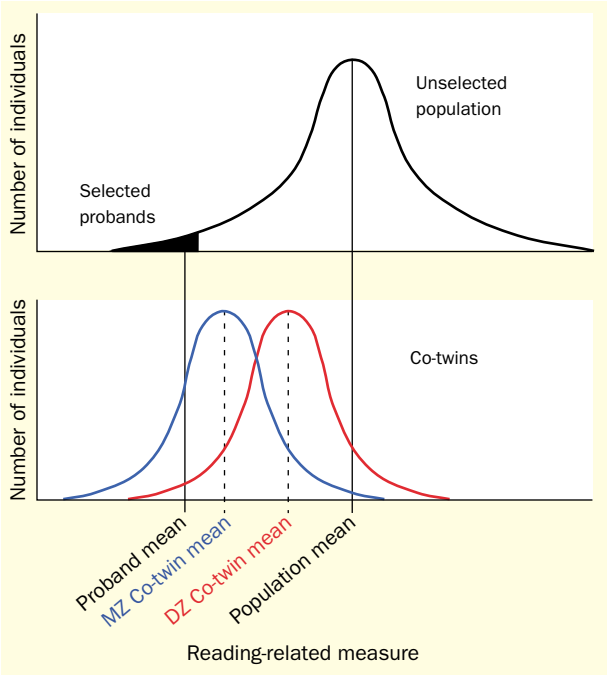

Figure 1. Measuring the importance of genetic factors in poor reading. The distribution of a hypothetical reading-related measure is shown for a population of twins, and also in monozygotic (MZ) and dizygotic (DZ) co-twins of reading-disabled probands. DeFries and colleagues[6] showed that the heritability of poor reading can be measured by quantification of the regression of co-twin scores towards the population mean as a function of twin-pair zygosity. The same framework can be used to provide a test of linkage at individual genomic loci within sibling pairs.

Despite this strong genetic involvement, dyslexia does not commonly segregate in families in a simple mendelian fashion.[3,12,34,38,40] Rather, ability to do reading-related cognitive tasks tends to decrease as a function of increasing genetic relatedness of relatives to the dyslexic probands. This finding suggests that several or many genetic factors determine reading ability, and that some or all of these factors might interact with one another to bring about particular influences on reading ability.[48–53]

Genetic dissection

Do different cognitive processes involved in reading develop independently of one another to some degree? If so, the existence of different genetic subtypes of dyslexia might be identified through epidemiological and gene mapping studies. In a pioneering study, Olson and colleagues[8] used a modification of Defries-Fulker regression (figure 1) on their Colorado twin data, in which probands were selected on one cognitive variable and co-twin regression was assessed on a different but correlated cognitive variable. The resulting bivariate estimates of heritability yielded a measure of the

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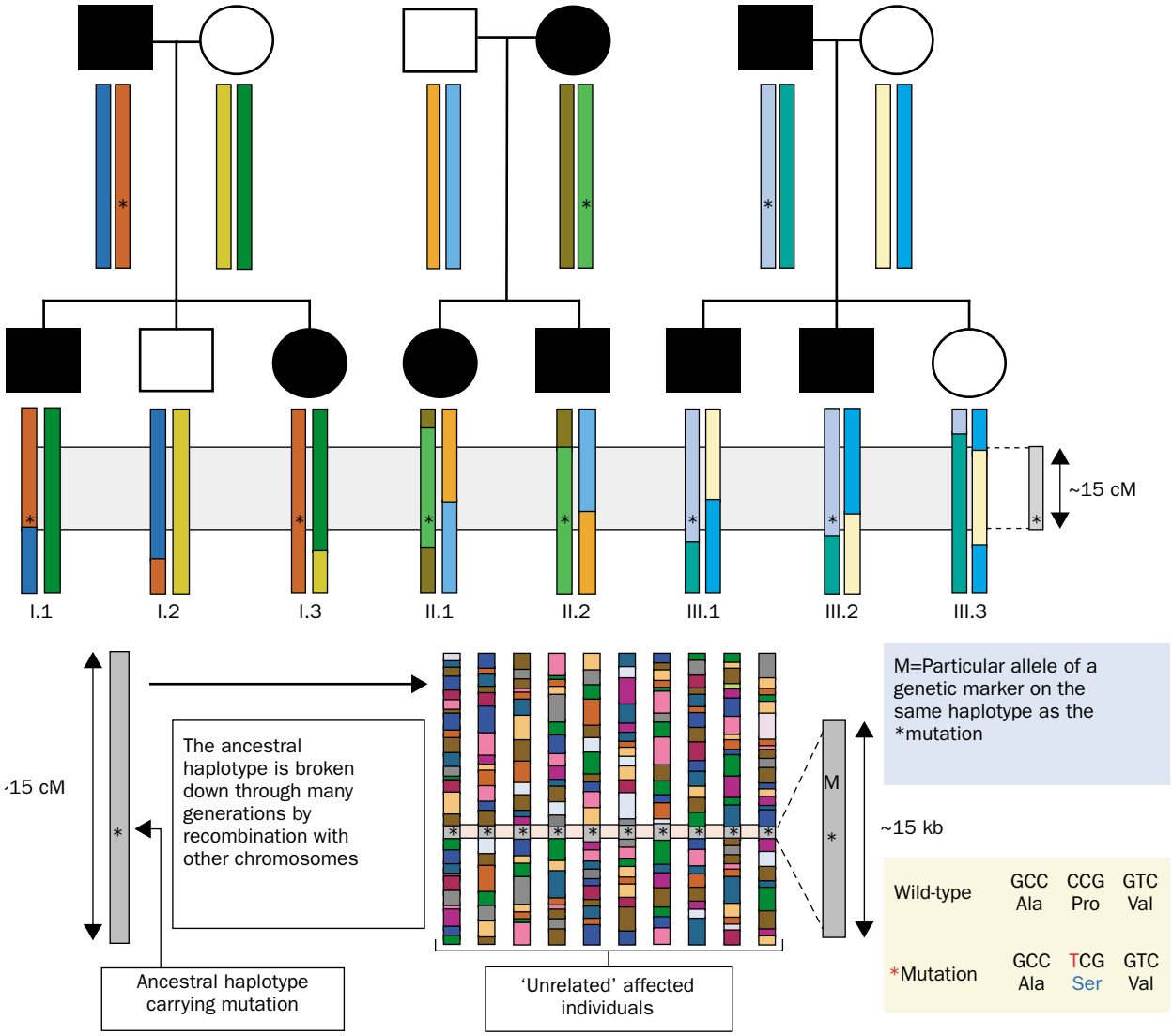

Figure 2. Top: traditional linkage analysis tests whether certain haplotypes are shared, within families, by individuals affected with a disorder more often than is expected by chance. In this example, all of the affected siblings (black symbols) in three separate families have inherited haplotypes that carry a disease mutation. With the assumption of a perfect genotype–phenotype correspondence, the region of linkage is defined by recombinations in individuals I.1 and II.2. Bottom: classic association analysis does not test for genotype–phenotype relations within families, but rather assumes that "unrelated" affected individuals may be descended from a common ancestor who carried a specific mutation.

degree to which the heritabilities of the separate measures were influenced by the same genes. The proportion of shared genetic variance between orthographic and phonological decoding skills was over 60%, as might be expected if these skills influence the development of one another during childhood learning, or else if the same neuronal systems partly underlie both processes.

Olson and colleagues[12] subsequently used a multivariate hierarchical regression technique to estimate the genetic and environmental influences on a first variable, genetic and environmental influences that are shared with a second variable, and genetic and environmental influences on the second variable that are independent from those of the first variable.[46] Significant independent heritabilites for orthographic coding (0·36) and phonological decoding (0·38) were identified, as well as further evidence for a shared genetic aetiology between the two measures. Interestingly, functional brain-imaging studies provide potentially congruent evidence for partly overlapping neuronal substrates for orthographic coding and phonological decoding.[31,54] For example, Rumsey and colleagues[31] identified a widespread region of left-hemisphere activation in normal readers that was common to both tasks, suggesting that both are processed to a large degree in a common neural network; however, the left superior temporal gyrus was more active in a phonological decoding task.

Gene mapping

Recent advances in high-throughput molecular genetic techniques and statistical methods have made possible

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several large-scale studies aimed at identification and mapping of the genetic variants that underlie individual differences in reading ability.[10,11] The identification of these genetic variants will allow more sophisticated analyses of the links between different reading-related cognitive, physiological, and behavioural measures than has been possible, which could lead to the identification of different aetiological subtypes of dyslexia on the basis of genetic data. In addition, new insights into the developmental mechanisms that underlie poor and normal reading will be gleaned from this research. For example, regions of the rodent or human fetal brain in which the relevant genes are actively expressed could be identified and the effects of the gene variants on neuronal cells or tissue studied in vitro.

However, the human genome contains roughly 35 000 genes distributed over 3 billion bp of DNA,[55,56] of which about half are expressed in developing or adult brains. Even if researchers use plausible biological hypotheses to limit the number of candidate genes to screen for mutations, thousands of genes still remain, and there is no guarantee that the developmental biology of dyslexia will conform to any given hypothesis. As a consequence, researchers have temporarily abandoned specific biological hypotheses in genetic studies of dyslexia,[11] and instead they have turned to linkage and association analysis (figure 2).

Mapping strategies

Over generations, homologous chromosomes are constantly divided and their sections are randomly recombined by the process of crossover during meiosis.[48,49] If a new mutation arises that causes susceptibility to dyslexia, it will, for a time, be inherited with a specific set of alleles representing any nearby polymorphisms on the chromosome. This set of alleles forms one particular extended haplotype that is a unique variant of that genomic region, but which undergoes steady attrition as more recombinations occur.[49] The inheritance of haplotypes can be tracked by analysis of polymorphic DNA markers, which need not themselves have any biological function.[48] The principle underlying both genetic linkage and association mapping is to test for non-random relations between phenotypic similarity across many individuals, and haplotype sharing between them, for the genomic regions of interest (figure 2).[48–51] The more generations that pass, the more powerful and accurate these analyses become, because each meiosis provides another opportunity for spurious genotype–phenotype relations to break down.

Linkage analysis refers to the analysis of individuals for whom family relations are known, whereas association analysis is used for large samples of unrelated individuals (ie, whose inter-relatedness is undefined, but who are presumed to share ancestry in the far distant past). Thus, linkage analysis makes use of only the limited number of meioses within defined pedigrees and does not depend on the identification of ancestral haplotypes (figure 2). By contrast, association analysis makes use of all of the crossovers that occur over many hundreds or thousands of generations. As a consequence, linkage analysis generally has less power than association analysis to detect genotype–phenotype relations within a study sample of a given size. However, linkage mapping can be done with many fewer genetic markers and is, therefore, easier to use in practice than association analysis.

Genome-wide linkage mapping can be carried out by analysis of about 400 highly polymorphic DNA markers (one at every 8 million bp of the genome).[10,33,57] However, for aetiologically complex traits, any linkage signals that are detected will remain of the order of 10 million to 30 million bp, spanning tens or hundreds of genes.[36,37,50,51,57,58] Association mapping, by contrast, has the power to focus on the specific causal DNA variants that influence phenotype variability but must, in most cases, be done with DNA polymorphisms at a maximum distance apart of only 15 000 bp (ie, 600–700 times more polymorphisms need to be analysed than are needed for linkage analysis).[59]

Studies so far

For the reasons described above, dyslexia researchers have tended to use linkage analysis in the first instance to identify broad genomic regions that contain tens or hundreds of potential candidate genes,[11] and association analysis is used within these defined regions. Various linkage studies have been done, and many regions of the genome that might harbour genetic variants that predispose to dyslexia have been identified.[10,11,34–37,44,45,60–71] Association studies within these regions of linkage, or the targeted screening of candidate genes for mutations, are in progress.

A difficulty with this research is the statistical issue of multiple testing. Linkage and association analysis both involve the testing of multiple genetic markers even within any one genomic region, let alone across the entire genome; furthermore, most researchers repeat these analyses for each of their full suite of cognitive reading-related measures.[10,34,35,37,39] Therefore, the researcher interpreting the current wealth of linkage data must apply the traditional epidemiological principles of replication,[72,73] a high threshold for positive significance, and consideration of different sample sizes to avoid being misled by false-positive linkage signals.

The most compelling linkage evidence for involvement in the determination of reading ability is for one locus on the short arm of chromosome 6 and another near the centromere of chromosome 18. According to commonly used guidelines,[73] linkage results can be categorised as weak (low significance), suggestive (moderate significance), or significant (surpassing the threshold p=0.05 when adjusted for testing of multiple genetic markers and phenotypic measures). The locus on chromosome 6 has shown weak or suggestive linkage in four independent family samples[34–37,44,45] of up to 89 families in each, although one study has failed to replicate this linkage.[39,60] The chromosome 18 locus has shown significant or suggestive linkage in three separate samples of at least 80 families.[10] In addition, these two loci have shown the two strongest linkage signals within the entire genome in our own study of 195 sibling pairs from the UK affected by dyslexia (figure 3).[10]

There is also linkage evidence that chromosomes 1, 2, 3, 13, and 15 contain loci that may influence reading ability.

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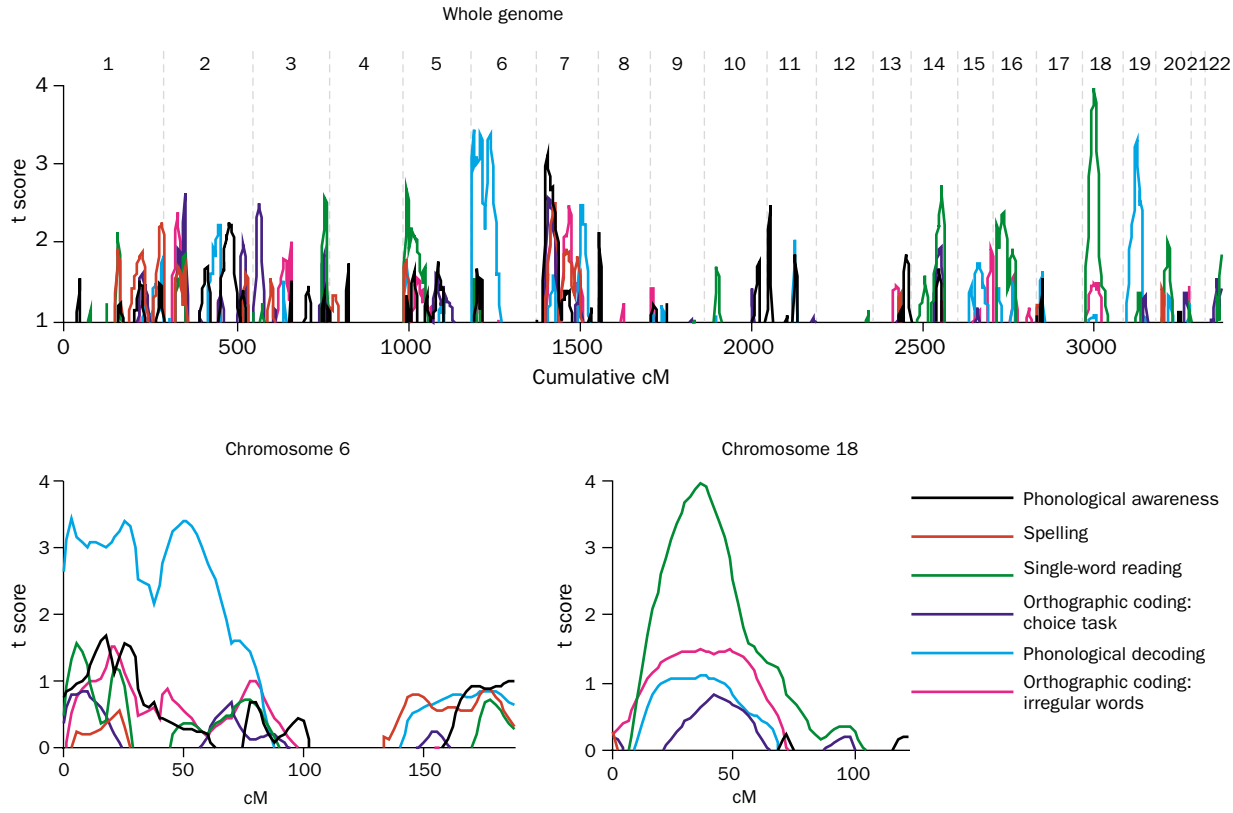

Figure 3. Can linkage results be used to dissect cognition? Top: autosomal linkage data from our genome-wide screen of UK sibling pairs, based on six measures of reading disability, and showing linkages to chromosomes 6p and 18p (and other non-replicated loci). These data were originally presented in Nature Genetics.[10] *Evidence for linkage is shown as t scores derived from basic DeFries-Fulker analysis. Chromosome identities are shown along the top. Bottom: although the loci on chromosomes 6 and 18 appear primarily to influence distinct reading-related measures, other studies have shown that both of these loci influence multiple measures of reading ability. A reliable genetic dissection of these measures will become possible only through linkage analysis of much larger samples, or else through the identification of the specific gene variants that underlie these linkage results. Reproduced with permission from Nature Publishing Group.[10] http://www.nature.com/neurosci/*

Each of these loci has been identified in a limited number of large families, but has also shown weak evidence for linkage in an additional larger sample.[10,34,60,71] Fisher and DeFries[74] provide an up-to-date, detailed review of genetic findings, complete with methodological critiques.

Limitations of linkage analysis

Our own genomewide linkage screen of UK siblings (figure 3) shows that the loci on chromosomes 6 and 18 both appear at first sight to influence distinct cognitive reading-related abilities. This finding could be interpreted simplistically as evidence for two cognitive subtypes of dyslexia, each influenced by variation at a discrete genomic locus. The initial impression from our analysis is that the locus on chromosome 6 influences phonological decoding ability and that the locus on chromsome 18 primarily influences single-word reading. However, these linkage results and others like them cannot be used to draw such conclusions as has been previously attempted.[34,35] This is a statistical limitation of the linkage method as commonly used in samples of about this size (195 sibling pairs).[36,75,76]

Linkage tests are done by modelling of a locus-specific effect on the overall variance in a phenotypic measure,[76,77] much as twin studies are used to estimate the overall heritability of such measures. Locus-specific effect estimates from linkage analysis can be biased upwards or downwards by random genetic sharing within subsets of the sample,[75,76] such that an accurate picture of the true effects that any given locus has across a range of correlated measures can be achieved only by replication and analysis in larger samples, or else by association analysis which is more powerful. Multivariate linkage methods are needed to test whether or not a given locus has a particularly strong effect on one measure and not on another, rather than simply comparing univariate linkage levels.

In another genome-wide linkage screen that we have done in 119 sibling-pair families from the USA,[10] we found that the loci on chromosomes 6 and 18 both appear to influence multiple reading-related cognitive traits, including orthographic and phonological coding abilities and single-word reading. This result has been further confirmed for the chromosome 6 locus by an additional study.[35] However, the statistical uncertainties involved in linkage analysis mean

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that we cannot yet measure accurately how much of the overall variability in reading ability these two loci account for, let alone whether they influence different cognitive measures to varying degrees.

Conclusion

One aim of molecular genetic research into dyslexia is to provide a better understanding of the specific problems that affect individual children with dyslexia, since there are subtypes of dyslexia that may be influenced by partly distinct genetic factors. Linkage mapping studies, the first of which have now been completed, are the first steps towards a molecular genetic dissection of dyslexia.[78] Genetic association studies are now under way,[58,79,80] targeted within the genomic regions identified by linkage analysis, and these studies promise to identify the specific gene variants that cause susceptibility to different subtypes of dyslexia. In practical terms, only when these variants are identified will researchers be able to measure accurately and compare the mean effects of different susceptibility alleles on the various cognitive, behavioural, and physiological measures related to dyslexia, and thus achieve a true genetic dissection of this complex trait.

The success of association-based approaches will depend on the nature and history of the polymorphisms that underlie susceptibility to dyslexia. Association approaches make the crucial assumption that a few common genetic variants cause variation in a trait.[59] If, by contrast, many rare variants underlie the linkages that have been found so far, association analysis may not have the power to detect these genetic effects. In that case, the only way to detect functional polymorphisms may be to screen exhaustively all of the genes within a linked region, in the hope that at least some of the important polymorphisms will produce overt disruptive effects on the genes containing them.

Identification of these genetic variants may mean that a child's particular risk of developing certain types of reading problems could be estimated before severe problems develop. Children might then be able to start individually tailored treatment earlier than is currently possible, and forewarned parents could watch more closely and respond more quickly to the first manifestations of the disorder.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed and references from relevant articles; articles were also identified through searches of the files of the authors. The search terms "dyslexia" and "reading disability" were used. Only papers written in English were reviewed.

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Authors' contributions

CF wrote this review, ILM produced the figures, and all three authors reviewed and revised the text.

Conflict of interest

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