

Genetic influences on language impairment and phonological short-term memory

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It has been known for some years that specific language impairment (SLI), an unexpected failure to acquire age-appropriate language skills, is highly heritable. However, molecular genetic studies have been hampered by the heterogeneity of the disorder and the predominant lack of clear genotype–phenotype relationships. We review recent studies suggesting that a better understanding of the genetics of SLI might emerge if we move away from clinical criteria for diagnosis to look instead at a theoretically based quantitative and cognitive measure of the phenotype: a test of phonological short-term memory (STM). Deficient phonological STM has been linked to specific genetic loci, and might play a role in determining some types of reading impairment as well as SLI. Identifying those cognitive deficits that work best as indices of heritable phenotypes will help us to uncover the aetiology of developmental disorders.

Introduction

Specific Language Impairment (SLI) is a failure to acquire age-appropriate language despite normal non-verbal intelligence and otherwise typical development [1,2]. Children with SLI often have limited vocabularies, produce immature speech sounds and use basic grammatical structures. Their sentences are short and simple and they may have difficulties following complex instructions. Many children with SLI struggle to learn to read and write, and even those who overcome early oral language difficulties are at risk of literacy problems [3].

SLI often runs in families, but there are seldom clear inheritance patterns. The case of the KE family, where a single autosomal mutation is associated with a distinctive pattern of speech-language disorder [4], is the exception rather than the rule. We suggest two reasons why this might be so: first, SLI is clinically heterogeneous, and second, SLI is likely to be influenced by several genes that interact, both with each other and with the environment, to produce an overall susceptibility to the development of disorder (i.e. a complex disorder). This means we are unlikely to make progress in understanding the genetics if we rely on conventional clinical diagnostic definitions that

lump together diverse children in a single clinical category. Rather, we need to use measures of the underlying cognitive basis of SLI in our quest for genotype–phenotype relationships. Here we describe recent studies that successfully adopted this approach, focusing principally on those using a measure of phonological short term memory (STM). This research not only advances our understanding of the aetiology of SLI; it also is starting to provide insights into the relationship between SLI and developmental dyslexia.

SLI as a deficit in phonological short term memory

There are numerous theoretical accounts of SLI, ranging from those that postulate a low-level auditory perceptual deficit [5] through to those that argue for a relatively discrete disorder affecting the development of grammar [6]. In 1990, Gathercole and Baddeley [7] proposed a different kind of theoretical account of SLI that regards it as a disorder of phonological STM.

The starting point for the theory is the finding that children with SLI perform poorly on measures of verbal STM, particularly on tests of non-word repetition (NWR) in which the task is to repeat meaningless sequences of speech sounds, for example, ‘*contramponist*’ [7–10]. The reason for this difficulty has been a matter of some debate: poor performance could reflect inadequate speech discrimination, impairment of speech-motor output processes, poor ability to segment phonemes, or weak vocabulary leading to lack of knowledge of frequent sound patterns. Gathercole and Baddeley, however, argue that the pattern of errors in children with SLI suggests that it is the memory component of the task that gives them most difficulty. Children with SLI are usually relatively unimpaired on short nonwords, but do much worse with longer items of 4 or 5 syllables [7,8]. Furthermore, the relationship between vocabulary level and NWR performance is weak at best in older children with SLI, and although there are clear effects of ‘word-likeness’ on children’s repetition of nonwords [11], this effect is comparable in children with SLI and typically-developing children [12].

NWR is also a sensitive test for detecting people with a past history of SLI who appear to have overcome their language limitations [8,13]. It is thought to be a good measure of residual problems because the participant

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cannot rely on previously learned knowledge to do the task.

Evidence for genetic influence on phonological STM: behavioural studies

A first step towards identifying genetic influence on a disorder is to see whether it runs in families. There is ample evidence that relatives of language-impaired individuals are at increased risk of developing SLI, and family members often report literacy difficulties [14,15]. Twin studies (see Box 1) consistently find that monozygotic twin pairs are linguistically more similar to each other than dizygotic twins, indicating that shared genes play an important role in susceptibility to SLI [16–19].

Bishop *et al.* argued that if weak phonological STM is an underlying cause of SLI, then it might make sense to define the phenotype in terms of NWR rather than in terms of conventional language tests. Using a method known as DeFries–Fulker analysis (Box 1) it was confirmed that deficient NWR is heritable [8].

The twin method can be taken further to test different theoretical accounts of SLI. As noted above, a popular theory of SLI attributes it to auditory perceptual problems [5], raising the question of whether deficient phonological STM might be secondary to a more basic perceptual difficulty (Figure 1). Bishop *et al.* [20] gave twins a test of NWR and a nonverbal auditory task based on Tallal's theory. We might anticipate that the two tests would turn out to be different ways of assessing the same underlying deficit, but this is not the case. Children with SLI are poor on both measures, but whereas deficits in NWR are highly

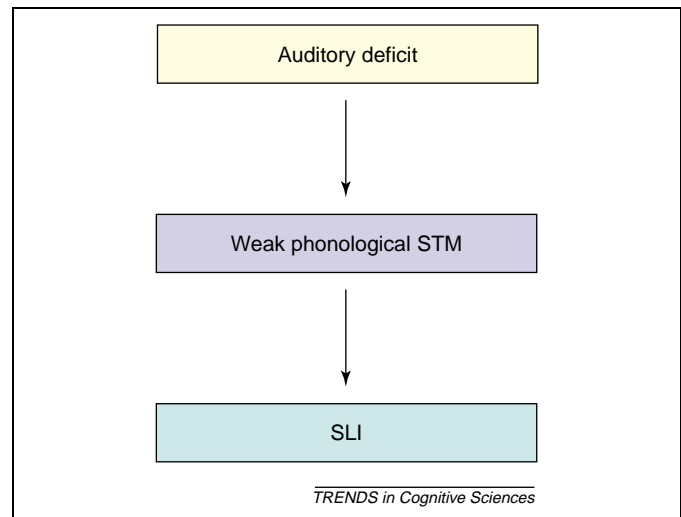


Figure 1. A simple bottom-up model of the relationship between auditory deficit, weak phonological STM and SLI. The theory put forward by Baddeley *et al.* [23] proposes that weak phonological STM leads to SLI by retarding vocabulary learning and acquisition of grammar. In this simple model this theory is integrated with Tallal's [5] suggestion that phonological deficits in SLI involve failure to analyse incoming speech at a fine enough grain because of auditory temporal processing limitations. This would lead to non-optimal encoding of phonological information in memory using syllable rather than segment-based chunks.

heritable, deficits on the nonverbal auditory task, appear to be heavily influenced by environmental factors. An exploration of causal influences pointed to musical experience at home as one possible factor [21]. Recently, Bishop *et al.* used similar techniques to consider the relationship between NWR deficits and syntactic difficulties in SLI [22]. Twins were given a NWR test alongside tasks designed to target the kinds of syntactic deficits that characterise SLI (see Figure 2). Both measures are highly heritable, but there is little overlap between the two kinds of deficit, which appear to have different genetic origins. In addition, there is no evidence of common aetiological origins for impairments of NWR and vocabulary, with

Box 1. Methodologies used in twin studies

Monozygotic (MZ), or identical, twins share their entire DNA whereas dizygotic (DZ), or non-identical, twins are genetically no more similar than a normal sibling pair. MZ and DZ twins reared together are likely to resemble one another because they share many environmental influences. However, if genes are important in determining a given disorder, we would expect MZ twins to be more similar to each other than DZ twins. Twin studies select twin pairs on the basis of a single twin, who is affected by the disorder under study, and calculate the likelihood that their co-twin is also affected (the 'concordance rate'). Increased concordance rates in MZ twins over those in DZ twins imply that genes play a role in the disorder under study.

An alternative way in which one can use twins to assess the importance of genes in a disorder is the DeFries–Fulker regression method [47]. This involves the selection of twin pairs in which one twin scores below a certain cut-off on a continuous trait. If poor performance depended on chance factors specific to the individual, then we would expect the mean score of co-twins to regress back to the population mean. If environmental factors common to both twins affect scores, then twins and co-twins should resemble one another, regardless of zygosity, and for both MZ and DZ twins, the mean co-twin score should be below the population mean. If genes are important, then we would expect MZ twins to resemble each other more closely than DZ twins, and the extent to which the scores of the co-twins regress back to the population mean will be a function of zygosity (MZ versus DZ). The method can be extended to consider whether the same genes are implicated in two heritable traits, by doing a bivariate analysis, in which twins are selected for poor scores on measure X, and then seeing whether the scores of their co-twins on measure Y can be predicted, and whether zygosity affects this prediction. See [48] for a more detailed explanation of this method as applied to verbal and nonverbal measures.

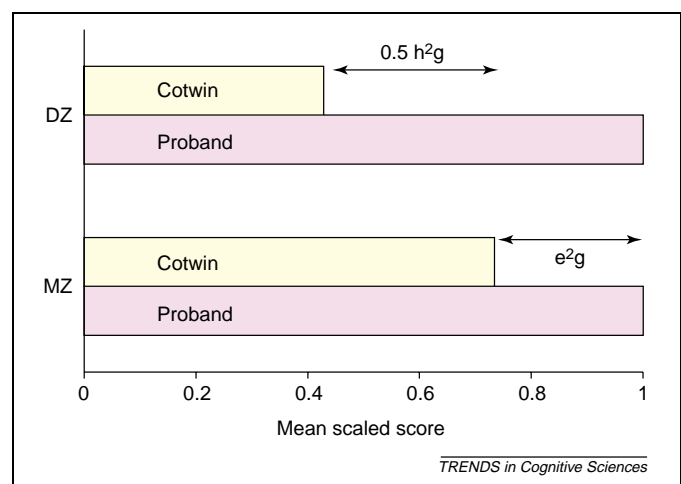


Figure 2. Nonword repetition data used in DeFries–Fulker analysis. Phonological STM means for MZ and DZ 6-year-old twins [22]. Probands were defined as those who scored in the lowest 13% on a measure derived from a NWR task. Scores have been transformed for DeFries–Fulker analysis so that the proband means equal one and the population mean is zero. Heritability of phonological STM deficit (h_g^2) is estimated as twice the difference between MZ and DZ co-twin means. Idiosyncratic environmental influences (including measurement error) (e_g^2) is the difference between MZ proband and co-twin means. Effect of environmental influences shared by both twins is obtained by subtraction: $c_g^2 = 1 - h_g^2 - e_g^2$.

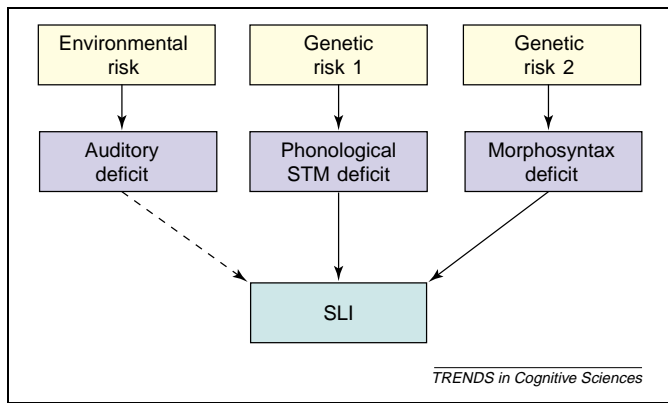


Figure 3. A risk-factor model of the aetiology of SLI. Rather than being different manifestations of the same underlying disorder, auditory, phonological and morphosyntactic deficits have distinct causes, and each deficit increases the probability that clinically significant SLI will result. Children with two or more deficits are most at risk. The dotted line from auditory deficit to SLI indicates that the causal path is weaker than for the two genetically based deficits.

the latter showing negligible heritability. These results challenge a simple model that maintains that poor phonological STM leads to SLI by retarding vocabulary learning and acquisition of syntactic rules [23]. It may be that it has its most marked effects, not on acquisition of linguistic knowledge, but on on-line processing of verbal material. An analogy can be drawn with mental arithmetic: despite knowing all the relevant number facts, it is possible to fail on a complex mental arithmetic problem because one is unable to keep all the relevant information in mind. Perhaps poor NWR is a hallmark of a comparable problem affecting linguistic processing, whereby the child fails to use language knowledge effectively because of inability to retain transient representations.

Given that different aetiologies appear to affect deficits in auditory processing, phonological STM and syntax, one might wonder if these correspond to different subtypes of SLI, with the syntactic version corresponding to the 'grammatical-SLI' postulated by Van der Lely [24]. However, the reality seems more complex, because in practice children can have any one of these deficits without being identified as a case of frank SLI. Rather, it is those children with more than one deficit who are most likely to receive a clinical diagnosis [20,22], suggesting a risk factor model such as that shown in Figure 3. Studies such as these emphasize the heterogeneity and multifactorial nature of SLI.

Molecular genetic studies of language disorders and phonological STM

Given that NWR appears to be a useful measure of a heritable phenotype, how do we discover the genes that influence this trait? Discovering genes for complex disorders usually begins with a genome screen to identify regions of a chromosome that show significant linkage to a disorder – that is, a Quantitative Trait Locus (QTL) (see Box 2).

There are three groups working on linkage studies of SLI and, to date, four possible QTLs have been identified across the genome [25–29]: *SLI1* on chromosome 16q, *SLI2* on chromosome 19q, *SLI3* on chromosome 13q

Box 2. Linkage, genome screens and QTLs

For most complex disorders, the initial step in gene identification usually takes the form of a **genome screen**. This approach allows one to position the relevant genes on a chromosome without any previous knowledge as to the disease pathology, the number of genes involved or the nature of the inheritance pattern.

A genome screen samples stretches of DNA that serve no specific function and show considerable variation from one individual to another. These can be used as 'markers' in **linkage analysis**, where one looks for regions that are shared by affected siblings more often than expected by chance alone. In its simplest form, linkage analysis categorizes individuals as affected or unaffected, but it can also be used with quantitative scores, in which case one searches for regions in which there is a correlation between the phenotypic score and the level of sharing between siblings. The method of linkage analysis will depend upon many factors including the phenotype under study, the samples available, and the way in which disorder is defined.

The probability that a given region is involved in a disorder is often reported as the **logarithmic odds ratio** or **LOD score**. This is the probability of the given data arising if the region is linked to a disorder, against that if the given region is not linked to a disorder. For a whole genome screen of a complex disorder, a LOD score of above 3.6 is usually considered significant. However, because the LOD score can be affected by variables such as the distribution of the trait and sample sizes, many researchers choose instead to report **empirical p-values**. These are derived from simulations of the data in hand and represent the probability of finding a given result within that specific dataset. In a perfect scenario, a LOD of 3.6 has a p-value of 2×10^{-5} [49]. Regions implicated by genome screens are known as a **Quantitative Trait Loci (QTLs)**.

It is important to recognize that finding linkage is not the same as finding a gene; rather, it is a way of narrowing the search by identifying chromosomal regions likely to harbour relevant genes. Any given QTL will contain many genes, only one of which underlies the linkage.

and *SSD* on chromosome 3p. We will focus on the three QTLs that have shown linkage to a NWR phenotype.

In 2002, the SLI Consortium completed its first genome screen in 98 families ascertained from both clinical and epidemiological sources, all containing at least one child affected by SLI [25]. The strategy was to search for correlations between three quantitative measures of language and a measure of genetic similarity between sibling pairs. Two QTLs were identified, both of which bordered on the level required for 'significant' linkage (Box 2). One of these, *SLI1* on chromosome 16, was linked specifically to NWR (LOD=3.55, empirical p-value = 0.00003), whereas the other, *SLI2* on chromosome 19, was specific to a measure of expressive language, the CELF-R [30] (LOD=3.55, empirical p-value = 0.00004).

Because linkage analysis involves multiple statistical tests, there is always a concern that spurious linkages may arise, and replication is therefore important. Indeed, findings of linkage to different measures in separate samples is not uncommon and often results from chance factors and small sample sizes [31].

In 2004, the SLI Consortium replicated linkage at both loci in a further 86 families [26]. The linkage on chromosome 16 again appeared to be specific to NWR (LOD=2.84, empirical p-value = 0.011) (Figure 3); however, this time chromosome 19 was also found to be linked to NWR (LOD=2.31, empirical p-value = 0.019), but not to the expressive language scale. Note that because replication studies involve the testing of a more restricted

set of genetic markers, the threshold for significant LOD scores is reduced.

Stein *et al.* [29] focused on a related phenotype, Speech-Sound Disorder, diagnosed when a child has difficulty producing speech sounds correctly for no known physical reason. This phenotype can overlap with SLI and reading disability, although it can occur in isolation from broader language and literacy difficulties [32]. The authors noted that ~50% of children with SSD encounter later difficulties with language, reading and spelling. Families in their study were given a large battery of tests which were used to derive an articulation factor, a phonological factor (with loadings on NWR and multisyllabic word repetition), and a vocabulary factor. They focused on a region of chromosome 3, previously identified as being linked to dyslexia, and found significant linkage between this region and the phonological (empirical p -value = 0.0002) and articulation (empirical p -value = 0.0015) factors.

Taken together, these studies indicate that the locus on chromosome 19 is likely to influence processes important in many language-related tasks, whereas a gene on chromosome 16 might influence a more specific system that could be crucial to phonological STM. It is possible that the chromosome 3 locus has similar effects to that on chromosome 16, but the fact that it also was linked to an articulation factor suggests that its influence may be more on accurate programming of phonological sequences rather than retention of phonological material in memory.

Phonological processing deficits in developmental dyslexia

Traditionally, SLI and developmental dyslexia have been regarded as separate disorders. However, there is now growing recognition that problems with oral and written language frequently co-occur, and many experts regard SLI and dyslexia as different manifestations of the same underlying disorder (see [3] for a review). This raises the question of whether the phonological STM theory of SLI could also account for dyslexia in children who do not have overt difficulties with oral language.

There is a widespread consensus among reading researchers that phonological processing deficits are a factor in many dyslexic cases, and some have gone so far as to propose that dyslexia should be *defined* as a phonological deficit [33,34]. However, most of this research has focused on problems with phonological awareness: the ability to segment spoken words into component sounds that map onto print. Consider the words *hit*, *hat* and *hot*: they all have the same initial and final phoneme, but there are acoustic differences in the initial and final portions of the speech waveform corresponding to these words, and no obvious dividing line between the three phonemes. Literate people can easily segment each word into consonant-vowel-consonant and could readily spell an unfamiliar sound sequence such as '*hent*'. For the child learning to read, none of this is obvious, and some children can readily repeat words such as '*hit/hat/hot*', and identify that they are different, but nevertheless are unable to identify the sounds within the words that correspond to individual letters. Children with dyslexia typically have

major problems in reading or writing unfamiliar non-words, and in doing tasks that involve manipulating speech sounds, even if such tasks involve no written language [35].

Although most research on phonological processing in dyslexia has focused on the analytic skills required to do phonological awareness tasks, there is evidence that there are often also limitations in phonological STM [36–38]. This suggests that literacy acquisition may be hindered not just by difficulty analysing the speech sounds in words, but also in retaining a segmented sequence of sounds in the course of decoding. Bishop and Snowling propose that many children have a core deficit in phonological processing that affects STM as well as phonological analysis, and that when this is a relatively isolated deficit the child will present with dyslexia, whereas when it is accompanied by additional oral language difficulties, affecting use of morphosyntax and/or oral comprehension, the clinical picture will be SLI [3]. Given that deficient NWR has been shown to be highly heritable in children with SLI, the question arises as to whether the same genetic factors are implicated in dyslexia.

Behavioural genetic studies of phonological STM deficits and literacy

Bishop [39] analysed data from literacy tests on the same sample of twins that had taken part in the study previously described [22]. In general, language and literacy deficits go hand in hand, and in children with SLI, the same causal factors appear to be implicated in both types of problem [39]. Nevertheless, in an unselected sample of twins from the general population a different pattern was seen: for those children with poor NWR, reading disability was heritable, whereas for other poor readers environmental factors were more important. A similar pattern has been seen in a new sample of 6-year-old twins [40]. A provocative interpretation of these studies is that reading impairment may be heritable only if it occurs in the context of weak NWR.

This conclusion agrees with work by Hsu *et al.*, who estimated parent-offspring and sibling-sibling correlations for various reading, spelling and language measures, and used a related measure as a covariate to obtain information about the interdependence of the paired measures on shared genetic factors [41]. This approach suggested that phonological STM, as assessed by NWR, accounted for a large proportion of the familial pattern of spelling [42].

Like SLI, dyslexia is a complex disorder. However, it is possible to use computer-based analyses with large datasets to deduce possible inheritance mechanisms by studying patterns of disorder across different generations of families. Using such methods to study performance in tests of digit span and NWR in dyslexic participants, Wijsman *et al.* estimated that 2 to 3 QTLs affect NWR performance [43]. The most parsimonious inheritance model involves a single 'major gene' which contributes heavily to NWR ability, working alongside a few 'modifying loci' which have smaller effects. Furthermore, they propose that at least one QTL may influence a memory component which is unique to the NWR task and does not

play a role in digit span. This is noteworthy, given that digit span is a less sensitive indicator of SLI than NWR [44], indicating that encoding of novel phonological material into memory may be particularly challenging for children with SLI. A separation of digit span and NWR is also supported by unpublished data from our group, which shows no significant linkage of digit span scores to *SLI1*. Such findings emphasise how genetic studies can clarify how apparently similar deficits may have different origins.

Molecular genetic studies of language and literacy impairments

To our knowledge, no linkage studies of dyslexia have directly analysed NWR. However, in studies of families affected by SLI, the SLI Consortium has analysed three reading-related measures: single-word reading, single-word spelling and reading comprehension. All show suggestive linkage to *SLI1* (LODs=1.49, 2.67 and 1.99 respectively) (Figure 4) [26].

In a more detailed investigation, the SLI Consortium performed multivariate linkage analyses across chromosomes 16 and 19 using a wide range of language

and literacy tests (unpublished data). Multivariate methods consider, not only the variance within each measure, but also the covariation between the various phenotypes. This additional information can be used to decipher the interactions between various measures at any given locus. These multivariate analyses indicate that whilst the linkage on chromosome 19 is influenced by a variety of tasks, the chromosome 16 locus depends upon a few selective measures (NWR, single word spelling and single word reading), each of which makes an equal contribution to the QTL.

Concluding comments

There is psychological and genetic evidence for a deficit of phonological STM in SLI. The *SLI1* locus on chromosome 16 represents a good candidate region for a gene implicated in this deficit. Once we discover the identity of the specific variant of a gene that increases the risk of poor phonological STM, this will help to elucidate the mechanisms underpinning this deficit and aid in the understanding of the aetiology of SLI and perhaps related disorders such as dyslexia (see also Box 3).

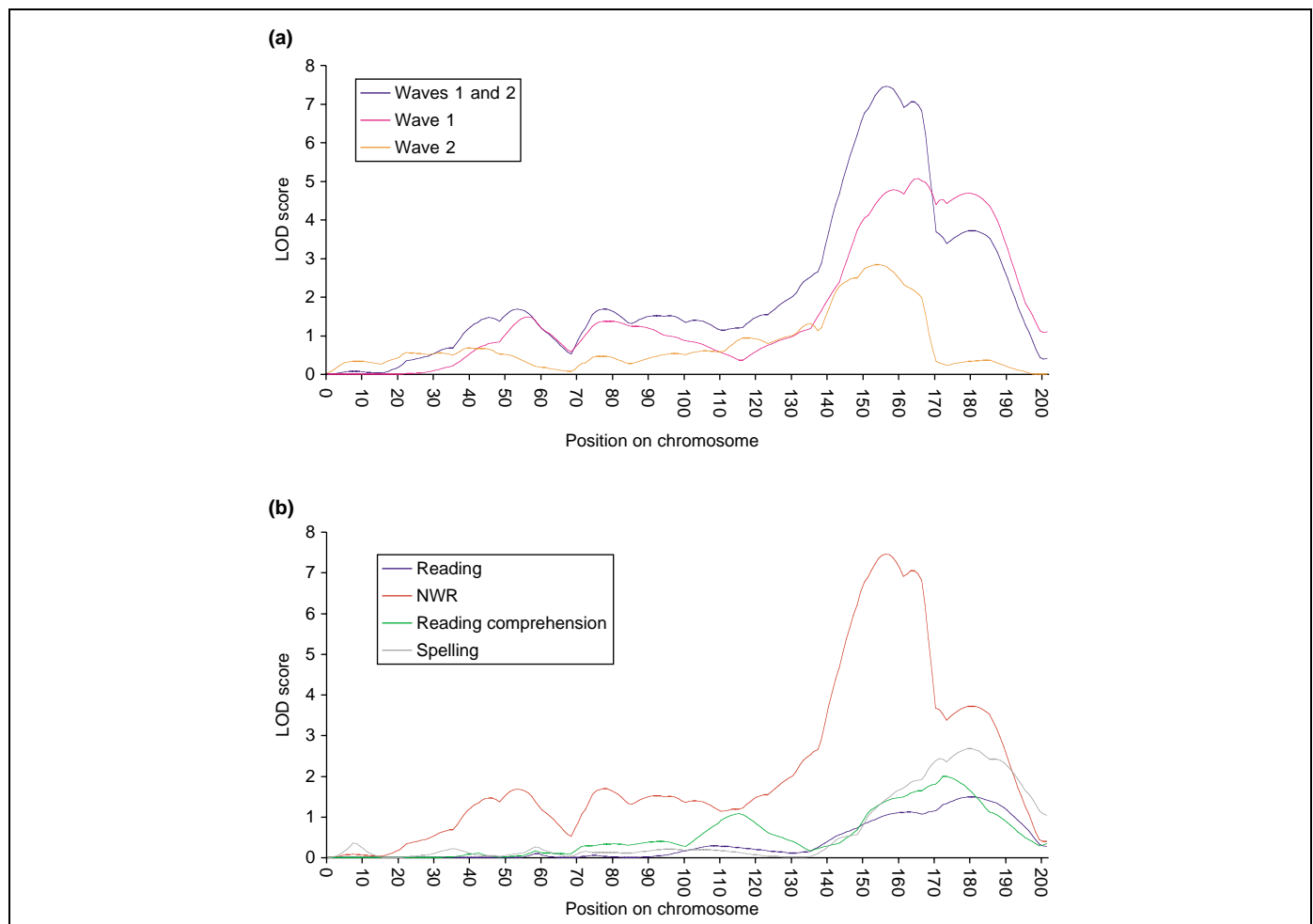


Figure 4. NWR Linkage to chromosome 16. Linkage is plotted as the LOD score across the length of chromosome 16. The higher the LOD score, the greater the likelihood that the genetic region contains a gene which influences the trait under study. The distance along the chromosome is measured from the tip of the short (p) arm (at position 0) through to the tip of the long (q) arm (at position 200). (a) Linkage of NWR trait to chromosome 16 in the two separate samples studied by the SLI Consortium [26], and the two samples combined (Waves 1 and 2). Linkage was found to occur at the same position in both samples and appeared to be specific to the NWR trait. (b) Linkage of NWR and reading traits within the combined wave 1 and 2 samples. Linkage was also found to three reading related measures within these samples. Adapted from [26].

Box 3. Questions for future research

- Are there common mechanisms underlying SLI and dyslexia?
- What is the gene on chromosome 16 and what biological processes is it involved in?
- How do the other identified genetic loci relate to *SLI1* and, between them, how do they control susceptibility to disorders such as SLI and dyslexia?
- Will we find different linkages if the phenotype is defined in terms of syntactic deficits?

It is important to emphasise that we are not claiming that all children with deficient nonword repetition have a heritable language impairment. Poor nonword repetition can arise for various reasons, and we know, for instance, that it is not associated with language difficulties when it is caused by mild hearing loss [12]. In preschool children, it appears to be affected by articulatory constraints as well as by memory limitations, and shows weaker heritability than in older children [45]. Many 5-year-olds with poor phonological STM do not go on to have language or literacy problems [46]. Even in a sample selected for language limitations, weak nonword repetition does not inevitably lead to SLI: two studies have now shown that the risk of SLI is much greater when poor nonword repetition is accompanied by another risk factor than when it occurs alone [20,22]. This suggests that one may need a 'double hit' in order for a clinically significant language impairment to be evident.

This leads us on to the next point. We emphasise that a genetic variant associated with poor nonword repetition would not be *the* gene for SLI. As noted above, it is likely that genes influencing SLI interact with one another and the environment, and that a specific variant confers an increased risk for impairment, rather than acting in a deterministic fashion. Furthermore, both SLI and dyslexia are heterogeneous conditions. In SLI, poor phonological STM appears to act as a good marker of a heritable phenotype, but it is not the only one [22]. In dyslexia, several significant linkages have been replicated [31]. As our understanding of phenotypes becomes more refined, we may be able to identify different subtypes with distinct aetiologies, but it seems unlikely that there will be clear one-to-one relationship between cognitive deficit and genotype, because many cases appear to have multiple deficits. Overall, the message from these studies is clear: to uncover the aetiology of developmental disorders, geneticists need to work together with psychologists to identify those cognitive deficits that work best as indices of heritable phenotypes. These are likely to be numerous, and will not necessarily map onto our conventional categories of disorder.

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