

Dissection of genetic associations with language-related traits in population-based cohorts

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Received: 28 April 2011 / Accepted: 24 July 2011 / Published online: 6 September 2011
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Abstract Recent advances in the field of language-related disorders have led to the identification of candidate genes for specific language impairment (SLI) and dyslexia. Replication studies have been conducted in independent samples including population-based cohorts, which can be characterised for a large number of relevant cognitive measures. The availability of a wide range of phenotypes allows us to not only identify the most suitable traits for replication of genetic association but also to refine the associated cognitive trait. In addition, it is possible to test for pleiotropic effects across multiple phenotypes which could explain the extensive comorbidity observed across SLI, dyslexia and other neurodevelopmental disorders. The availability of genome-wide genotype data for such cohorts will facilitate this kind of analysis but important issues, such as multiple test corrections, have to be taken into account considering that small effect sizes are expected to underlie such associations.

Keywords Epidemiology · Cognition · Language · Dyslexia · Quantitative genetics · Association studies · Neurodevelopmental disorders

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The genetics of language and reading disorders

Genetic factors are expected to contribute significantly to neurodevelopmental disorders. Recent advances in the field have been marked by the identification of several genes as susceptibility factors for dyslexia (or reading disability) and specific language impairment (SLI). Dyslexia is characterised by unexpected difficulties in learning to read, whereas SLI refers to difficulties in the acquisition of oral language (Pennington and Bishop 2009). In both disorders, a diagnosis is met in the absence of other co-occurring medical conditions (e.g., hearing loss for SLI) or neurological disorders (e.g., generalised learning disability) (Skuse et al. 1997). The biology of dyslexia and SLI remains largely unexplained, and the causes are expected to be the results of multiple interacting factors of both genetic and environmental origin affecting the early stages of brain development. It is estimated for both disorders that, the prevalence in first-degree relatives of affected individuals is 30–50%, compared to the general population prevalence of approximately 5–10% (Barry et al. 2007; Fisher and DeFries 2002). Dyslexia and SLI show extensive comorbidity. Estimates show that 40–55% of children diagnosed with either dyslexia or SLI meet criteria also for the other disorder (Snowling et al. 2000; McArthur et al. 2000). It remains an open question whether common genetic factors may contribute to clinically distinct disorders, partially explaining the consistently observed comorbidity (Pennington and Bishop 2009; Smith 2007).

Most of the candidate genes for dyslexia and SLI have been identified in family-based samples through genetic association studies targeting chromosomal regions previously mapped by linkage studies (positional cloning approach). These associations are characterised by p values that would not stand the magnitude of significance currently expected for genome-

wide association studies (GWAS; $P < 10^{-7}$). However, consistent replications in independent samples at the same locus and often with the same genetic markers provide robust support to these associations.

Candidate genes

Genetic linkage studies have identified several loci which may contribute to dyslexia including *DYX1* on chromosome 15q21, *DYX2* on chromosome 6p21, *DYX3* on chromosome 2p, *DYX5* on chromosome 3p, *DYX6* on chromosome 18p11, *DYX8* on chromosome 1p, and *DYX9* on chromosome Xq27 (Williams and O'Donovan 2006; Scerri and Schulte-Korne 2010). SLI linkage loci include *SLI1* on chromosome 16q, *SLI2* on chromosome 19q and *SLI3* on chromosome 13q (Newbury et al. 2005). Positional cloning, candidate gene analysis and translocation breakpoint mapping have pinpointed candidate genes within some of these linkage regions for both dyslexia (Scerri and Schulte-Korne 2010; Paracchini et al. 2007) and SLI (Newbury and Monaco 2010). Some of these genes have been analysed in population-based cohorts.

The first candidate gene proposed for dyslexia was *DYX1C1* (dyslexia susceptibility 1 candidate 1) (Taipale et al. 2003). The breakpoint of a chromosome translocation (t(2;15)(q11;q21)) co-segregating with dyslexia in a single family was located between exons 8 and 9 of *DYX1C1* (Taipale et al. 2003). In addition, two variants in *DYX1C1*, with a putative functional effect, were identified through association analysis in a sample of individuals with dyslexia (Taipale et al. 2003). Replication studies in independent samples selected for dyslexia have consistently reported modest size associations (Dahdouh et al. 2009; Cope et al. 2005a; Meng et al. 2005a; Marino et al. 2007; Brkanac et al. 2007; Scerri et al. 2004; Wigg et al. 2004). Many of these studies reported associations with an opposite allelic trend which could be due to differences in linkage disequilibrium patterns between populations (Scerri and Schulte-Korne 2010) suggesting that these two markers may detect a signal for a different genuine functional variant.

Two genes have been proposed for the *DYX2* locus following association analysis by fine mapping in this region in many independent samples selected for dyslexia (Scerri and Schulte-Korne 2010; Paracchini et al. 2007); *DCDC2* (Doublecortin domain containing) (Brkanac et al. 2007; Schumacher et al. 2006; Meng et al. 2005b; Harold et al. 2006; Newbury et al. 2011; Deffenbacher et al. 2004; Ludwig et al. 2008) and *KIAA0319* (Deffenbacher et al. 2004; Cope et al. 2005b; Francks et al. 2004). The associations with the *KIAA0319* gene are clustered around the first exon and a single variant has been shown to regulate the expression of this gene (Paracchini et al. 2006; Dennis et al. 2009).

The region spanning the *MRPL19* and *C2ORF3* genes was identified following fine mapping association analysis at the *DYX3* locus (Anthoni et al. 2007). Overlapping haplotypes across this region showed association with dyslexia in two independent samples of Finnish and German origin. These associations have not been replicated yet in independent studies.

The *ROBO1* (Roundabout 1) gene was identified through the breakpoint mapping of a chromosome translocation involving the *DYX5* locus in an individual with dyslexia (Nopola-Hemmi et al. 2001). A rare single nucleotide polymorphism (SNP) haplotype spanning *ROBO1* also segregated with dyslexia in a large multi-generational pedigree, where the *DYX3* linkage was originally identified (Hannula-Jouppi et al. 2005). However no evidence of association with common variants in larger cohorts have been reported so far, suggesting that *ROBO1* may be relevant only in isolated cases (Hannula-Jouppi et al. 2005).

The associations with SLI have all been identified in one and the same UK cohort collected by the SLI Consortium (SLIC) (SLI Consortium 2002). Two associations were identified by a high-density SNP screen in the *SLI1* region of linkage on chromosome 16 (Newbury et al. 2009). Two clusters of variants showed significant associations with the non-word repetition measure, which is a verbal short-term memory score and is regarded as a good marker for heritable SLI (Bishop et al. 1996). The first cluster fell within the *CMIP* (C-MAF Inducing Protein) gene and the second within the *ATP2C2* (ATPase, Ca²⁺ transporting, type 2C, member 2) gene. *CNTNAP2* (contactin-associated protein-like 2), on chromosome 7q, was proposed as a candidate for SLI after being identified as a downstream target of *FOXP2*, which has been implicated in severe and rare forms of language impairment (Lai et al. 2001). The SLIC cohort was used to evaluate the effects on language performance of the *CNTNAP2* gene, and found variants significantly associated with the non-word repetition task (Vernes et al. 2008).

In summary, association studies in clinical cohorts ascertained for reading and language disorders have led to the identification of different candidate genes for dyslexia and language impairment (Table 1). With some exceptions (*ROBO1* and *FOXP2*) the disorder-associated genetic variants in the genes listed above are common alleles which are normally found in the general population.

Comorbidity explained by genes?

Common genetic variants associated with reading and language disorders can be used directly to investigate whether genetic risk factors can explain the observed comorbidity between dyslexia and SLI. One recent study directly addressed this question by testing for association

Table 1 Candidate genes for dyslexia and SLI analysed in population-based cohorts

Gene	Disorder	Reference	Other phenotypes	Reference	Population Cohort	Associated phenotype	Reference
<i>DYX1C1</i>	Dyslexia	Taipale et al. 2003	ADHD	Wigg et al. 2005	Australian twins Raine	Reading	Bates et al. 2009 Paracchini et al. 2010
<i>KIAA0319</i>	Dyslexia	Cope et al. 2005b; Paracchini et al. 2006	Language	Newbury et al. 2011; Rice et al. 2009	ALSPAC Australian twins	Reading	Paracchini et al. 2008; Scerri et al. 2011a Luciano et al. 2007
<i>DCDC2</i>	Dyslexia	Schumacher et al. 2006; Meng et al. 2005b	ADHD	Couto et al. 2009	ALSPAC Australian twins	Reading	Scerri et al. 2011a Lind et al. 2010
<i>ROBO1</i>	Dyslexia	Hannula-Jouppi et al. 2005	Autism	Anitha et al. 2008	Australian twins	Reading, Language	Bates et al. 2011
<i>CMIP</i>	SLI	Newbury et al. 2009	Reading	Newbury et al. 2011	ALSPAC	Reading	Scerri et al. 2011a
<i>CNTNAP2</i>	SLI	Vernes et al. 2008	ADHD Autism	Elia et al. 2010 Alarcon et al. 2008; Arking et al. 2008	Raine	Language	Whitehouse et al. 2011

the same panel of SLI or dyslexia associated SNPs in cohorts selected for either SLI or dyslexia (Newbury et al. 2011). *CNTNAP2* and *CMIP* were found to be associated with reading measures but only in the SLI cohort, suggesting that a pleiotropic effect on multiple traits would be dependent on a background of language impairment. *KIAA0319* was the only gene that showed association with reading measures in both the dyslexia and SLI cohorts; in addition it was found to be associated with language measures in the SLI cohort. These findings both support the role of *KIAA0319* in contributing to reading skills and suggest that this gene may also contribute to language abilities. This last observation is in agreement with an independent study that reported *KIAA0319* to be associated with language-related measures in a different cohort of language impaired individuals (Rice et al. 2009). Interestingly, rare variants at the *DYX2* locus in between *KIAA0319* and *DCDC2* have been found to be associated with speech perception in children with dyslexia (Czamara et al. 2011).

Candidate genes for dyslexia and language impairment have also been reported to be associated with other disorders (Table 1). *CNTNAP2* has been consistently implicated in autism with both common (Alarcon et al. 2008; Arking et al. 2008) and rare rearrangements (Rossi et al. 2008; Bakkaloglu et al. 2008; Poot et al. 2010; Jackman et al. 2009). One of these studies reported a specific association with the “age at the first spoken word” measure (Alarcon et al. 2008), which provides an indication for late language development. Language impairment is a distinctive symptom of autism. *CNTNAP2* has also been associated with attention deficit/hyperactivity disorder (ADHD), Gilles de la Tourette syndrome (Verkerk et al. 2003), mental retardation (Ballarati et al. 2009; Zweier et al. 2009), schizophrenia and epilepsy (Strauss et al. 2006; Friedman et al. 2008), and selective mutism (Stein et al. 2011).

Variants in *ATP2C2* (Lesch et al. 2008) and *DCDC2* (Couto et al. 2009) have been associated with ADHD, and *ROBO1* showed reduced gene expression in some autistic cases (Anitha et al. 2008).

Taken together, these studies suggest that candidate genes underlying SLI and dyslexia may contribute to other conditions in particular those with a neurodevelopmental origin, such as autism and ADHD. Most of these genes have been shown to be specifically expressed during the development of the human foetal brain and, in particular, a role in neuronal migration has been proposed for many of the dyslexia candidates (Paracchini et al. 2007; Galaburda et al. 2006). Neuronal migration is an important process at the basis of cortex development which will determine the correct location of neurons across the different cortical layers. Therefore it would be expected that genes controlling such a general mechanism would have broad phenotypic effects rather leading to specific conditions. However, the evidence for pleiotropic effects, with the exception of *CNTNAP2* which is robustly supported, are mainly based on weak associations reported in isolated studies which still require replication. One of the main limitations of these studies is the small sample size. The effect of a particular gene may be enriched in a particular sample on a particular phenotype and, without adequate power, effects on other phenotypes might be hindered. An additional complication is the high variability of psychometric measures used across multiple studies which makes replication more difficult.

Replication studies in population-based cohorts

Population-based cohorts characterised with both genetic data and quantitative cognitive phenotypes offer a very

valid alternative to investigating the role of dyslexia and SLI candidate genes (1) (Table 1). These are usually relatively large longitudinal cohorts with the main advantage of presenting a wide range of cognitive phenotypes in most individuals. Independent studies have shown that the effect of some dyslexia and SLI candidates can be detected on the normal range of variation observed at population level using quantitative approaches. Therefore, providing that this observation is valid for most of the susceptibility genes, population-based cohorts can help to elucidate whether these genes affect specific traits or have wider effects.

Three main cohorts have been employed so far for such studies, one in the UK and two in Australia. The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort consists of over 15,000 children from the southwest of England that had expected dates of delivery between 1 April 1991 and 31 December 1992 (Golding et al. 2001). From age 7, all children were invited annually for assessments on a wide range of physical, behavioral, and neuropsychological traits, including reading and language-related measures. DNA is available for approximately 11,000 ALSPAC children while cognitive phenotypes are available in 3,000–7,000 of those.

One Australian cohort is twin-based, but also includes non-twin siblings, and was recruited in the greater Brisbane area (McGregor et al. 1999). Genome-wide SNPs data and phenotypes are available in >1,100 individuals.

Lastly, the Raine Study, is a pregnancy cohort that was recruited in Western Australia around Perth (Newnham et al. 1993). From the original cohort of women, 2,868 of their children have been followed over the last two decades with detailed assessments performed every 2 to 3 years. Both genome-wide SNPs data and cognitive measures are available in >500 individuals.

KIAA0319 was the first gene to be analysed in population-based samples and was found to be associated with measures of single word reading or single word spelling in both the ALSPAC (Paracchini et al. 2008) and the Australian twin cohort (Luciano et al. 2007). Both studies reported association with the same SNPs and haplotype previously reported to be associated with dyslexia (Francks et al. 2004), but it has to be noted that the associations in the Australian sample was with an opposite allelic trend. Both studies concluded that the *KIAA0319* candidate gene for dyslexia contribute to the general reading abilities, supporting the idea that dyslexia can be considered as the lower tail of the phenotypic distribution across the entire population. The Australian twins have also been analysed for other dyslexia candidate genes. *DCDC2* was associated with measures of single word reading and single word spelling but with SNPs that differed from the original reports in clinical samples (Lind

et al. 2010). Associations with reading and spelling measures were reported also for a SNP located in one *DYX1C1* exon, implying a putative functional effect (Bates et al. 2010). However, this SNP (rs17819126) failed to show association in previous studies (where it was named 271 G>A) (Taipale et al. 2003; Scerri et al. 2004). Common variants spanning *ROBO1* were also analysed in this cohort for both reading and language measures (Bates et al. 2011). Given the rarity of the dyslexia-associated haplotype, *ROBO1* has not been selected for replication and this is the most comprehensive follow-up study for this gene so far. The strongest signals were for non-word reading and the related digit-span forward task assessing verbal short-term memory while only weaker signals were reported for the reading measures.

Single gene analysis for SLI candidates was conducted for *CNTNAP2* in the Raine sample (Whitehouse et al. 2011). The same pattern of SNP associations previously reported for SLI (Vernes et al. 2008) was associated with the early stages of language development in children from the general population.

Two other studies analysed specific common variants across different candidate genes. The first study was conducted in the Australian Raine cohort and analysed SNPs in candidate genes for dyslexia for association with reading and spelling measures (Paracchini et al. 2010). SNPs previously associated with dyslexia were selected for *DYX1C1*, *KIAA0319*, *DCDC2* and *MRPL19/C2ORF3*. An initial signal in *DYX1C1* was supported by associations with other SNPs across this gene.

In the second study the same four dyslexia loci and the two SLI candidates *CMIP* and *ATP2C2* were tested for association with different reading and language related measures in the ALSPAC cohort (Scerri et al. 2011a). *KIAA0319*, *DCDC2* and *CMIP* showed association specifically with single word reading and single word spelling. These observations suggest effects on specific cognitive functions opposed to a contribution on multiple traits. Therefore, this study does not support the hypothesis that *KIAA0319* contributes to language skills at population level, but does not exclude that such effects may be restricted to individuals with a background of language impairment (Newbury et al. 2011; Rice et al. 2009). Similarly, *CMIP* and *ATP2C2* did not show association with language abilities in the general population ALSPAC sample, while an association with non-word repetition was detected in an ALSPAC subgroup selected for being language impaired (Newbury et al. 2009). Instead, the association of *CMIP* with single word reading is supported by similar findings in the SLIC cohort (Newbury et al. 2011).

In summary quantitative analyses on cognitive measures available for population-based cohorts have been useful for

replicating genetic associations with candidate genes for dyslexia and SLI discovered in clinical samples. In addition, the availability of different phenotypes has helped to interpret the associations and formulate novel hypothesis about the cognitive functions controlled by these genes.

Beyond replicating associations

Two recent studies illustrate further how population-based cohorts can be used to dissect genetic associations with cognitive traits (Scerri et al. 2011a, b). Both studies were based on the ALSPAC sample that, given the large sample size, has the power to apply explorative approaches. The study that analysed both dyslexia and SLI candidate genes addressed several questions in addition to testing for association with different reading and language-related traits (Scerri et al. 2011a). One of these questions was whether the associations observed for *KIAA0319*, *DCDC2* and *CMIP* were truly with general reading abilities in the normal range or might have been driven by the individuals with the most severe phenotypes. To test this hypothesis a subgroup of children meeting criteria for a dyslexia diagnosis was identified and then excluded from quantitative association analysis. While *KIAA0319* and *CMIP* showed the same degree of association with reading abilities as in the initial sample, the associations with *DCDC2* tended to disappear suggesting that the signal observed originally in the entire sample was actually due to a small proportion of individuals meeting a clinical diagnosis for dyslexia. This hypothesis was supported by a case-control analysis conducted on the same subgroups of children classified with dyslexia in the ALSPAC population. The same subgroup of individuals meeting the dyslexia criteria were compared with controls showing high scores on the reading test. While *KIAA0319* and *CMIP* show weak or no association, *DCDC2* yielded the strongest signal supporting a specific role in contributing to dyslexia. The same case-control setting allowed testing the effects of comorbidity on the associations. The subgroup of children with dyslexia was enlarged to include the children with dyslexia together with SLI and/or ADHD. Case control analysis with this larger sample led to stronger associations with the *DCDC2* gene. These results suggest it is important not to exclude individuals with comorbidity for SLI or ADHD when designing association studies of dyslexia. Generally, comorbid individuals are excluded from ascertainment to obtain samples as homogeneous as possible. Conversely, these data would suggest that the effect of genes on reading skills is the same even in the background of clinically distinct disorders. If similar findings could be generalised they may help to better understand the biology of comorbidity, and in this case they would suggest that the

same cognitive deficit leads to reading impairment regardless of clinical classifications.

The second study was carried out using ALSPAC as a replication set for an association with handedness (Scerri et al. 2011b). *PCSK6* was found to be associated with a quantitative measure of relative hand skill measured with the peg-board test (Annett 1985) with a GWAS conducted in individuals with dyslexia. *PCSK6* is a very attractive candidate for handedness because of a known interaction with *NODAL* in establishing left–right asymmetries early in development. The same gene showed a weak trend of association in an independent sample of individuals with dyslexia. Not many other samples are available with both reading and peg-board measures and ALSPAC, being one of those, was selected for further replication. Therefore, analysis was conducted in the same subgroup of individuals with dyslexia described in the previous study (Scerri et al. 2011a). Not only did *PCSK6* yield a significant association with handedness in this subgroup providing a robust replication, but it also led to a very intriguing finding. Analysis of *PCSK6* in the larger ALSPAC sample, representing the general population, was still significant but with an opposite allelic trend. Specifically, each copy of the minor allele of the associated SNP (rs11855415, minor allele frequency [MAF] ~20%) was associated with a relative higher right-hand skill in individuals with dyslexia and, conversely, the same allele was associated with a reduced variability in relative hand skill in the population sample. While the association in the general population requires to be replicated in independent studies, it does reinforce the observation that the effect of *PCSK6* differs in people with neurodevelopmental disorders (Fig. 1). For many decades, researchers have tried to establish the relationship between handedness and psychiatric disorders. Handedness can be considered a reflection of cerebral asymmetries and right-handedness implies a dominance of the left hemisphere for motor function. Following Paul Broca's (1861) observation in 1861 of a patient whose aphasia was caused by a left hemisphere lesion, there has been significant interest in looking for a link between language, laterality and handedness. Several theories have been proposed to explain this link and handedness has been suggested as a consequence of the evolution of language (Corballis 1991). More recently, neuroimaging work has shown that abnormal asymmetries are found in individual with dyslexia (Leonard and Eckert 2008). Despite considerable efforts, no convincing association has been found between either hand preference or hand skill and neurodevelopmental disorders (Bishop 1990; Francks et al. 2003). The *PCSK6* finding opens new line of investigations to understand the link between handedness, cerebral asymmetries and reading abilities and suggest that the picture is more complex than what was anticipated and

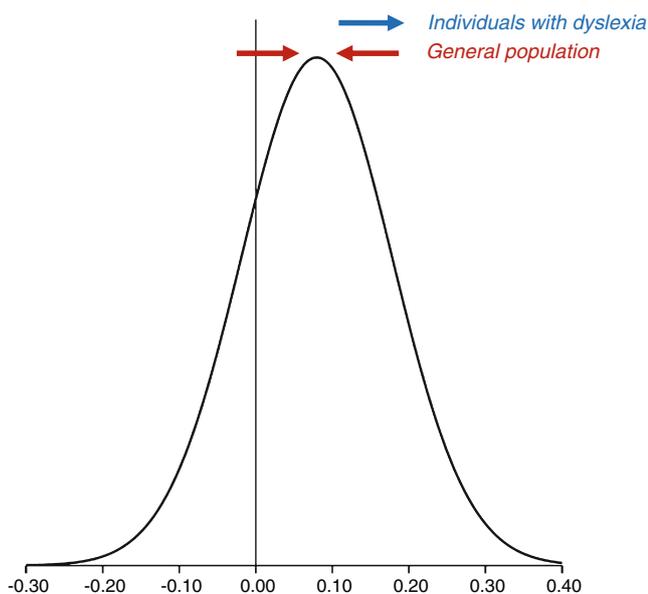


Fig. 1 Representation of allelic trend for the association of *PCSK6* with handedness. A quantitative measure for relative hand skill (PegQ) is normally distributed in the population with a positive mean score. PegQ is derived from measurements taken with the peg-board task which assess the time taken by the subjects to move a row of pegs from one location to another with the left hand (*L*) and right hand (*R*) separately. From these data, PegQ is derived with the formula $[2(L - R)/(L + R)]$, where a negative score indicates relative higher skills with the left hand and a positive score indicates relative higher skills with the right hand. Carriers of the minor allele of rs11855415 tend to be more skilled with their right hand if they have dyslexia, while they tend to score around the mean of PegQ if they do not have dyslexia (general population sample)

cannot be reduced to the simple measurement of left-handed frequency among patients.

Genome-wide challenges

Generating genotype data for large samples is no longer an issue from an experimental nor a financial point of view. The real bottleneck in genetic studies is now becoming the availability of samples properly phenotyped samples. GWASs have been successful in mapping many disease-associated genes but the success is largely dependent on adequate sample sizes (Donnelly 2008). Genome-wide SNP data are now available for the three cohorts described here and it is important to consider how to handle these data. While it would be tempting to use a genome-wide analytical approach for cognitive traits, several issues need to be considered. First of all, such cohorts were not designed to conduct genome-wide scans for discovery experiments and do not have adequate power to lead to significant findings. Power calculations show that a sample of 5,874 individuals is required to detect a genetic effect contributing to at least 1% of the total phenotypic variation,

assuming a MAF of 10% (Purcell et al. 2003). ALSPAC in principle would have the adequate power for detecting such an effect but larger samples are required if multiple phenotypes are entered in the analysis. Therefore, until larger samples will be available, current population-based cohorts should be used to follow-up established associations and test-specific hypotheses rather than conducting discovery studies.

Concluding remarks

The identification of candidate genes associated with reading and language disorders is an important milestone in our understanding of the underlying biology (Smith et al. 2010). However, this is only an initial step and extensive molecular characterisation is required to properly interpret these associations. The use of population-based cohorts has proved to be a useful tool to further dissect genetic association. First of all, such cohorts represent valid tools to replicate original association. In addition, the discovery that some genetic variants associated with dyslexia do influence reading abilities in the normal range of variation provides significant support to the idea that dyslexia can be viewed as the lower tail of a phenotypic distribution across the population rather than a categorically defined condition. Analysis with multiple cognitive traits that are available in population cohorts can shift the association with a disorder (i.e., dyslexia) to more subtle phenotypes (i.e., single word reading) leading to a more precise mapping of the affected cognitive function. These approaches can also help to elucidate whether genes have a very restricted effect on specific traits or impact more generally on cognition according to the hypothesis of the generalist genes (Plomin and Kovas 2005).

Language-related disorders are complex and caused by the interplay of multiple factors of both genetic and environmental origin. The genes described here are likely to represent only a minor component of the causative elements. It is essential to consider these elements together with findings from other disciplines in order to start visualizing the bigger picture. Functional imaging has started to factor in genetic variants to evaluate directly their impact on cognition. For example, *CNTNAP2* variants associated with autism (Alarcon et al. 2008; Arking et al. 2008) and language impairment (Vernes et al. 2008) have recently been associated with frontal lobe connectivity (Scott-Van Zeeland et al. 2010). Functional characterisation of genes involved in rare and severe form of language impairment, such as *FOXP2*, may help to elucidate biological pathways relevant to milder and more common forms of related disorders. Epigenetic regulation of gene expression could play a role in neurodevelopmental

disorders. Changes in DNA methylation have been implicated in processes like learning and memory through rapid and dynamic changes (Tsankova et al. 2007). Disruption of the epigenetic machinery in the brain leads to Rett Syndrome, and increasing evidence is supporting the role of epigenetic changes in neurodevelopmental conditions including mental retardation and schizophrenia, making a strong case for an involvement in language-related disorders. Therefore a multidisciplinary approach and the integration of findings from different research area are clearly a high priority in the study of language disorders.

Acknowledgements The author was supported by the Wellcome Trust [076566/Z/05/Z]; [075491/Z/04] and the Medical Research Council [G0800523/86473]. The author thanks Dianne Newbury and Tom Scerri for useful comments to the manuscript. The Merrill Advanced Studies Center provided the opportunity to present and discuss this work at the Annual Merrill conference.

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