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GENETICS IN SOLVING DYSLEXIA PUZZLES

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SUMMARY

Background:

Developmental dyslexia, or specific learning difficulties, is the most common neurobehavioral disorder affecting school-aged children, with a prevalence rate of 5-17.5%. Family and twin studies have pointed to a genetic component in the etiology of dyslexia. However, dyslexia is a complex disorder at both the genetic and environmental levels, and its nature so far remains unclear.

Results:

Dyslexia is thought to be a "complex trait" determined by a number of genes, each with small to moderate effects on the specific phenotype, involving various factors such as heterogeneity, incomplete penetrance, phenocopy, or oligogenic inheritance. Based on combined linkage and association analyses using both qualitative and quantitative phenotypes, multiple regions (DYX1-DYX9) on chromosomes 1, 2, 3, 6, 11, 13, 15 and 18 have been reported likely to contain genes contributing to dyslexia. Most recently four candidate genes (DYX1C1, KIAA0319, DCDC2, ROBO1) have been identified as associated with dyslexia.

Conclusions:

In this review, we focus on the genetic basis of dyslexia and provide an overview of several of the most susceptible loci on chromosomes and prominent candidate genes currently suspected of conditioning dyslexia.

Key words: candidate genes, genetic linkage, heritability, familial prevalence

INTRODUCTION

Developmental dyslexia, also called “specific learning difficulties,” is a disorder characterized by an unexpected difficulty in reading that cannot be explained by intelligence deficit, sensory deficit or lack of learning opportunity and motivation. In Poland, the most commonly used definition of developmental dyslexia is the one standardized by Prof. Marta Bogdanowicz, a pioneer in this field of research. According to this definition, dyslexia is a syndrome of disturbances of higher mental activities that manifest themselves as specific difficulties with learning to read and write. They are conditioned by partial disturbances of the psychomotor development of the functions involved in reading and writing and their integration. Among the developmental deficiencies of cognitive function that determine the possibility of verbal communication, the most essential are language function disturbances, including the phonological aspect of the language (Bogdanowicz 2003). According to ICD-10 (WHO 1992), dyslexia is not the direct result of other disorders, such as mental retardation or milder impairments in general intelligence, gross neurological deficits, uncorrected visual or auditory problems, emotional disturbances, or inadequate schooling. However, some of the clinical features of dyslexia may overlap with other disorders, such as alexia (acquired reading disorder), language learning disability (Vicari et al. 2005; Ziegler et al. 2005) or attention-deficit hyperactivity disorder (ADHD) (Willcutt et al. 2007). Phonological deficits, however, are characteristic only for dyslexia (Shaywitz 1998).

Dyslexia appears to be the most common neurobehavioral disorder affecting school-aged children and adults. However, the prevalence of this disorder remains uncertain, ranging from 5% to 17.5%, according to varying reports in the literature (e.g. Shaywitz 1998; Shaywitz et al. 1990). The precise number of individuals with dyslexia is probably an arbitrary figure, since this disorder exists on a continuum from severe cases to milder forms of dyslexia and cannot be clearly separated from the general population, where levels of reading and spelling proficiency are normally distributed. Undoubtedly, the lack of precise diagnostic criteria also makes it inordinately difficult to estimate the real number of children affected by dyslexia. In the case of languages with quasi-transparent orthography (i.e. a relatively close and consistent phoneme-grapheme relationship), the diagnosis is even more complicated because it relies only on reading speed. And although dyslexia occurs in all known languages, its diagnostic frequency varies among languages (Lindgren et al. 1985, Paçhalska et al. 2010): for example, it is more often diagnosed in English than in Italian. The male/female gender ratio for dyslexia has also been part of the debate. Although most previous studies have suggested that dyslexia affects both males and females equally (Rumsey 1992), some recent epidemiological studies indicate a twofold preponderance of dyslexic boys compared to girls (Grabowska & Bednarek 2004;

Rutter et al. 2004; Liederman et al. 2005). Shaywitz et al. (1990) argued that the observed difference was the result of a biased approach, while others (Olson 2002; Hawke et al. 2006) have suggested that the sex ratio depends on several factors, including IQ and severity of the reading deficit, so that more severe selections may increase the ratio of males to females.

There still remains much space for discussion about the nature of this disorder and the precise definition of dyslectic phenotypes. The latter task is particularly difficult, because most longitudinal studies have indicated that dyslexia involves an extremely stable developmental disturbance which does not, contrary to popular opinion, completely disappear with adolescence (Shaywitz et al. 1999). Although many adults with dyslexia can develop normal standards of reading, still, the disorder remains apparent through poor reading fluency (Lubs et al. 1993). Moreover, affected individuals quite often reach a much lower level of education than would be expected, based on their level of intelligence, and because of this disorder they are subjected to much greater psychosocial stress (Maughan 1995).

The first case of “congenital word blindness” (as dyslexia was then called), was diagnosed over 100 years ago (Hinshelwood 1895; Morgan 1896), but despite intensive studies, the molecular and developmental etiology of this disorder has remained unclear. Dozens of research groups have investigated heritability, models of transmission, and the genetic background. During the past decade, progress in human genetics has made it possible to identify chromosomal sites that could be determining factors for a predisposition to dyslexia. If we can uncover how specific genetic variants relate to variability in different cognitive skills, such as phonological awareness and orthographic coding, we will be able to understand the nature of dyslexia, quickly diagnose it, and determine the proper therapy. In this review, we focus on the genetic basis of dyslexia and provide an overview of several susceptibility loci on chromosomes and prominent candidate genes suspected of conditioning dyslexia.

THE GENETIC BASIS OF DYSLEXIA

The familial nature of dyslexia was first noted at the beginning of the twentieth century (Thomas 1905), and since then, it has been consistently supported in a number of twin- and family-based studies (e.g. DeFries et al. 1987; Lubs et al. 1993; Schulte-Körne et al. 1996; Grigorenko 2001; Fisher & DeFries 2002; Demonet et al. 2004). In one of the first, an interview-based study of 120 families, Hallgren (1950) postulated familial and autosomal dominant inheritance of dyslexia. This familial nature of dyslexia, with genetic heterogeneity, was also confirmed by studies based on psychometric tests (Finucci et al. 1976). For the child with an affected parent, the risk of dyslexia has been estimated as 40-60%, and it increases when other members of the family are also affected (e.g. Pennington et al. 1991; Pennington & Gilger

1996; Schulte-Körne et al. 1996; Ziegler et al. 2005). In clinical twin studies it has been shown that the concordance rate for reading disability is higher in monozygotic twins (up to 68%) than in dizygotic pairs (up to 38%) (Cardon et al. 1994; DeFries & Alercon 1996). However, if genes were the only cause of dyslexia, monozygotic twins would always share dyslexia and approximately half of the dizygotic twins. The observed genetic pattern indicates that there are significant environmental influences as well (e.g. Shaywitz & Shaywitz 2005). However, the average proportion estimates for genetic and environmental influences may differ depending on component skills in word reading (Gayan & Olson 2001). For example, the phenotypes of dimension word reading (up to 58%) and spelling (70%) are thought to be the most strongly influenced by genes (Gayan & Olson 2001; Olson 2002). Interestingly, the genetic influences are supposed to be more important as a cause of dyslexia in children with high IQs than in those with low IQ (Knopik et al. 2002).

Nowadays, at the genetic level dyslexia is assumed to be a "complex trait" that does not show classical Mendelian inheritance, but is determined by a number of genes, each with small to moderate effects on the specific phenotype (e.g. Lewitter et al. 1980; Pennington et al. 1991; Lander & Schork 1994; Schulte-Körne, 2001; Chapman et al. 2003). The lack of simple phenotype-genotype correlations in dyslexia may result from various factors (Fisher et al. 1999; Démonet et al. 2004). First, it is suggested that dyslexia is genetically heterogeneous and different genetic backgrounds may influence the trait in different families (Pennington et al. 1991; Lubs et al. 1993). Another reason for the lack of correlation may be incomplete penetrance, which causes the disorder not to develop even though some predisposition alleles have been inherited. Furthermore, there are age-dependent variations in penetrance and expressivity, with many dyslectics showing compensation by the time they reach adulthood (Fisher et al. 1999). On the other hand, phenocopy (non-hereditary variation) may be observed where as a consequence of environmental factors (or other random factors) the disorder develops without a specific predisposing allele. Oligogenic inheritance is also suggested, when the disorder depends on the simultaneous presence of predisposition alleles at several multiple loci and interactions between them contributing to the increased risk of dyslexia. If we assume that the various cognitive processes involved in reading develop independently of one another to some degree, the different genetic subtypes of dyslexia could be identified. Whether the differences in the genetic loci represent polygenic inheritance, different cognitive paths to the same phenotype, or different subtypes of dyslexia is not clear.

There are, in principle, two main strategies to elucidate the genetic basis of dyslexia. The first starts from the phenotype and ends with the genotype, and is intended to test nonrandom relations between the phenotypic similarity of many individuals, and haplotype sharing between them, for the genomic regions of interest. The second strategy begins with a known genotype and

by examining the phenotype tries to find any elements specific for individuals and families, which are then used to define a particular group or a subgroup. Current studies have been concentrated on the first research strategy; the second is a promising approach for the future.

Genetic linkage analysis, the first strategy, refers to studies of individuals with dyslexia for whom family relations are known. Linkage analysis aims to identify broad regions within chromosomes that may include tens or even hundreds of potential candidate genes specific to dyslexia. It is assumed that dyslexia is “linked” to a gene or genes in a given region if siblings with a significant higher genetic similarity in this region are more likely to have this disorder. But this does not mean that a particular “linked” region is responsible for all or even most cases of dyslexia. The results from many different linkage analyses for dyslexia suggest that, because of the number of different regions and related genes, each of these genes may be responsible for a few cases of dyslexia in the population, and what is more, the specific genes may be different for different people (Smith et al. 1991; Fisher & DeFries 2002; Pennington & Olson 2005).

Linkage mapping studies are the first step towards understanding the molecular basis of dyslexia. The next step is genetic association analyses, which are now under way, targeted within genomic regions identified by linkage analysis. These studies aim to identify the specific gene variants that could be correlated with different subtypes of dyslexia. In practical terms, only the identification of these variants would make it possible to assess and compare the mean effects of different susceptibility alleles on the various cognitive, behavioral, and physiological measures related to dyslexia, leading to the identification of different etiological subtypes of this disorder. By contrast to linkage analysis, association analysis is used for a large sample of unrelated individuals, for example, whose inter-relatedness is undefined, but who are presumed to share ancestry in the far distant past. As a consequence, association analysis is generally more useful than linkage analysis to detect genotype-phenotype relations within a study sample of a given size. On the other side, linkage analysis is easier to use in practice, because it can be conducted with many fewer genetic markers.

LINKAGE REGIONS IN DYSLEXIA

Recent advances in molecular techniques and statistical methods have enabled several large-scale studies aimed at identification and mapping of the genetic variants that underlie individual differences in reading ability (e.g. Fisher & Smiths 2001; Fisher & Francks 2006). Based on combined linkage and association analyses using both qualitative and quantitative phenotypes, multiple chromosomal regions have been reported likely to contain genes contributing to dyslexia. As with all complex disorders, not all linkage findings are completely overlapping between independent studies. In the following

sections an overview of chromosomal regions has been presented, along with some suggested candidate genes appearing there which, according to the present state of knowledge, show links with dyslexia.

Chromosome 15 – DYX1 and the DYX1C1 gene

A possible link has been identified between dyslexia and a variation around the centromere of chromosome 15 (Smith et al. 1983). Although this result has not been confirmed by subsequent research (e.g. Bisgaard et al. 1987), the studies have been continued, and later discoveries pointed to the role of the 15q15-21 region in the etiology of dyslexia (e.g. Smith et al. 1991; Schulte-Körne et al. 1998; Grigorenko et al. 1997, Schulte-Körne et al. 1998; Morris et al. 2000; Chapman et al. 2004; Marino et al. 2004). According to the guidelines of the International Gene Nomenclature Committee, this locus has been described as DYX1 (dyslexia-susceptibility-1). Although a number of studies have pointed out a link or association on this chromosome, the precise locations differ; some studies show 15q15.1 (Morris et al. 2000, 2004; Marino et al. 2004); others, 15q21 (Grigorenko et al. 1997, Schulte-Körne et al. 1998; Nöthen et al. 1999; Chapman et al. 2004).

Based on analyses of this region, evidence of linkage for word reading and phenotype dimension (Smith et al. 1983; Chapman et al. 2004) and spelling (Schulte-Körne et al. 1998; Nöthen et al. 1999) have been found. Also, family-based association mapping showed positive association within this region (Morris et al. 2000). Interestingly, region 15q21 has also shown evidence of linkage to attention deficit hyperactivity disorder (ADHD, Bakker et al. 2003).

In the search for a candidate gene, the karyotype analysis of one Finnish family appeared significant, the members of which, suffering from dyslexia, all had translocation t(2;15)(q11;q21) (Nopola-Hemmi et al. 2000). Gene DYX1C1 (dyslexia-susceptibility-1, candidate-1; originally called EKN1), which lies in chromosome breakpoint 15q21, was suggested as the first gene related to dyslexia (Tiapale et al. 2003). DYX1C1 encodes a nuclear tetratricopeptide repeat domain protein, found in cortical neurons and white matter glial cells, but its function has not yet been thoroughly examined (Tiapale et al. 2003). It has been shown that mutations in this gene could result in abnormal neuronal migration of rodent neocortex and disrupted auditory processing (Wang et al. 2006). In a wider Finnish population, two presumably functional variants within the DYX1C gene, -3G-to-A and 1249G-to-T, have been reported as significantly associated with dyslexia (Tiapale et al. 2003). Exchange for -3A could alter the gene's expression because it was found in a regulatory place, whereas 1249T caused stop codon creation, as a result of which a shorter DYX1C1 protein was synthesized (Tiapale et al. 2003).

Further studies, conducted outside of Finnish populations, have not confirmed the role of DYX1C1 variants in increasing the risk of dyslexia (e.g. Scerri et al. 2004; Wigg et al. 2004; Cope et al. 2005b; Bellini et al. 2005; Marino et al. 2005; Meng et al. 2005a). However, in two cases (British and Canadian samples), sig-

nificant association has been shown with the opposite two-marker haplotype compared to Taipale et al. (2003) (Scerri et al. 2004; Wigg et al. 2004).

This failure to replicate can be explained by the genetic heterogeneity of dyslexia in different populations; however, it does not seem plausible that -3A and 1249T alleles could be linked with dyslexia only and exclusively in the Finnish population. We may rather be observing something like undiscovered etiological variants in *DYX1C1*, or changes in another coupling gene, inherited together with -3G-to-A and 1249G-to-T alleles. On the other hand, the reason may lie in methodology, e.g. incorrect selection of the control group or too small a number of analyzed cases, so that the Finnish associations could represent false positives (Fisher & Francks 2006). It is recommended to continue a search for a gene linked with dyslexia in the *DYX1* region.

Chromosome 6 – *DYX2* (two candidates: *KIAA0319* and *DCDC2*) and *DYX4*

The most significant linkage evidence for involvement in the determination of reading ability is reported for loci on the short arm of chromosome 6 (Smith et al. 1991; Cardon et al. 1994; Grigorenko et al. 1997; Fisher et al. 1999; Gayan et al. 1999; Grigorenko et al. 2000; Kaplan et al. 2002; Turic et al. 2003; Deffenbacher et al. 2004). Most of the linkage/association studies have converged particularly on part of 6p23-21.3, known as the *DYX2* locus (dyslexia susceptibility 2). Based on analyses of this region linkage has been found for phonological and orthographic processing (Fisher et al. 1999; Gayan et al. 1999; Kaplan et al. 2002). Unfortunately, so far „risk alleles” have not been identified with any certainty. What is more, there is no unanimity about one specific gene being responsible for dyslexia. The results of some research point at the *KIAA0319* gene (Francks et al. 2004; Cope et al. 2005a), whereas others suggest the *DCDC2* gene (doublecortin domain containing protein 2) (Meng et al. 2005b). Moreover, some studies have failed to replicate the linkage at all (Field & Kaplan 1998; Nöthen et al. 1999; Petryshen et al. 2000). Apart from these studies, there has not been much research in which two candidate genes undergo simultaneous analysis, which is crucial for understanding the relative contribution of both genes and describing their mutual interaction (Deffenbacher et al. 2004; Harold et al. 2006; Ludwig et al. 2008). Harold et al. (2006) reported a combined analysis of *KIAA0319* and *DCDC2* in a British cohort and found a strong association only with the first gene. On the contrary, Ludwig et al. (2008) in their *KIAA0319* and *DCDC2* in a German sample obtained no significant evidence for interaction between *KIAA0319* and dyslexia itself. However, they found nominally significant results for the sub-dimension word reading, which may be seen as evidence for interaction between the two genes.

Within the 6p22 region, 3 genes – *THEM2*, *TTRAP* and *KIAA0319* – have been located. The first of these codes a metabolic track enzyme, and the product of the second takes part in key processes in the cell, such as apop-

tosis or immunological response. Both genes are widely expressed. In contrast KIAA0319 undergoes expression mainly in the cerebral neocortex of developing mouse and human brain tissue, and codes a protein which appears to regulate interactions and adhesion between adjacent neurons (Fisher & Francks 2006).

Positive evidence for association with reading-related parameters in the region of the KIAA0319/TTRAP/THEM2 gene cluster has been reported for independent British and American samples (Deffenbacher et al. 2004; Francks et al. 2004; Cope et al. 2005a). Francks et al. (2004) found the strongest association at the single-marker and haplotype level within KIAA0319 and TTRAP, whereas Cope et al. (2005a) pointed out the strongest association especially within KIAA0319. In the British group examined by the latter two studies, SNPs have been discovered in this gene which seemed to be best linked with dyslexia. One of them causes alanine-to-threonine substitution in the product of the KIAA0319 gene. Nevertheless, this substitution is also common in the unaffected group, and is not characteristic of risk haplotypes linked to dyslexia. Generally speaking, it is rather unlikely that the substitution in the protein structure coded by KIAA0319 influences directly the occurrence of dyslexia. It has been shown that carriers of the assumed risk haplotype have a 40% reduction in the expression of KIAA0319, while maintaining a normal level of THEM2 and TTRAP expression (Paracchini et al. 2006).

Besides the evidence for association in the KIAA0319/TTRAP/THEM2 gene cluster, strong association with a single nucleotide polymorphism marker (SNP) was reported also for DCDC2, from another gene cluster in the region 6p22: VMP/DCDC2/KAAG1 (Meng et al. 2005b). Moreover, in a small group of affected individuals a deletion of ~ 2 kb has been identified in intron 2 of DCDC2, which encodes simple tandem repeats (STR) of presumed brain-related transcription factor binding sites (Meng et al. 2005b). In a study of German dyslexics, DCDC2 was examined at the SNP as well as the ~2 kb deletion level, and the association was also supported (Wilcke et al. 2009). Strong evidences for association with SNP polymorphism within DCDC2 was shown also by Schumacher et al. (2006a). However, in this study no functional risk allele was found, and the deletions observed by Meng et al. (2005b) were not analyzed at all. On the other hand, Harold et al. (2006) found only the deletion associating in a British cohort, as did Brkanac et al. (2007) in an American one. To sum up, of all polymorphisms, the deletion seems to show the most consistent results.

DCDC2 undergoes expression in many kinds of tissues, including fetal and adult brain regions (Meng et al. 2005b; Schumacher et al. 2006a). Its product, a cytoplasmatic protein, may take part in cortical neuron migration during brain development. The role of impaired neuronal migration in the etiology of dyslexia was also suggested by the findings of Wilcke et al. (2009). It appears that, similarly to the case of KIAA0319, changes in the DCDC2 gene sequence influence the regulation of its expression (Meng et al. 2005b),

although so far no functional experiments in humans seem to confirm this. However, it has been shown that inhibition of each of the two genes leads to poorer neuronal migration in the neocortex of fetal rats (Meng et al. 2005b; Paracchini et al. 2006).

Based on the chromosome-wide linkage study of a large Canadian multiplex family, another region, DYX4 (dyslexia susceptibility 4) has also been identified on chromosome 6; 6q11–q12 (Petryshen et al. 2001). Phonological coding and spelling have been noted as particularly linked with locus DYX4. Unfortunately, there has been no support of this finding in other independent studies.

Chromosome 2 – DYX3

Linkage analyses have identified region 2p15-p16 (DYX3, dyslexia susceptibility 3) as correlated with dyslexia (Fagerheim et al. 1999; Petryshen et al. 2002), as well as reported translocations on chromosome 1 (Froster et al. 1993). Currently, no phenotype components have been noted as particularly linked with locus DYX3.

Chromosome 3 – DYX5 and the ROBO1 gene

Linkage with markers in the region of DYX5 (dyslexia susceptibility 5), which lies in chromosome region 3p12–q13, has been described only in one four-generation Finnish family (Nopola-Hemmi et al. 2001). Dyslexia usually is treated as a complex trait, but this family model of transmission appeared to be consistent with autosomal dominant inheritance for a single gene.

In possible candidate gene identification in this region, the examination of unrelated persons with dyslexia who were carriers of the translocation t(3;8) (p12;q11) turned out to be very helpful (Hannula-Jouppi et al. 2005). The chromosome 3 translocation breakpoint includes the ROBO1 gene intron, localized in the linkage region 3p12. Interestingly, investigations of the orthologous gene in *Drosophila* (Robo) and mice (Robo1) indicate that ROBO1 (roundabout *Drosophila* homolog of 1) is an axon guidance receptor gene involved in neuronal connections between the two sides of the brain (Kidd et al. 1999; Andrews et al. 2006). On screening ROBO1 in a large Finnish family, DYX5-linked, it was discovered that its members with dyslexia are carriers of an unusual allele combination SNP (Hannula-Jouppi et al. 2005). One of these identified variants caused a change in the protein structure coded by ROBO1 through inserting/deleting an aspartic acid residuum. The examination of the level of ROBO1 gene expression in lymphocytes showed that the expression was reduced in persons with haplotype risk (Hannula-Jouppi et al. 2005). It has been suggested that this altered ROBO1 gene expression may predispose for dyslexia by decreasing the amount of this gene's product in the central nervous system. However, it is not certain that the data concerning decreased ROBO1 gene expression in lymphocytes can be also referred to brain tissue. It is also questionable that in one person with strong dyslexia

in the Finnish sample chromosome-3 translocation has not been found, although found in siblings (Hannula-Jouppi et al. 2005). It is not out of the question that their disorder is caused by a different etiological change in an undiscovered gene (Fisher & Francks 2006).

Chromosome 18 – DYX6

DYX6 (dyslexia susceptibility 6) was identified near the centromere in chromosome region 18p11 through a complete quantitative trait loci analysis based on a genome-wide scan in independent British family samples (Fisher et al. 2002). However, other studies have failed to detect this linkage (e.g. Schumacher et al. 2006b). So it seems likely that much larger linkage samples will be needed to dispel doubts.

Chromosome 11 – DYX7

The chromosome region 11p15 (DYX7, dyslexia susceptibility 7) has indicated linkage in only one Canadian family sample (Hsiung et al. 2004). DYX 7 has been suggested as a region contributing to dyslexia regarding the presence of the gene for the dopamine D4 receptor (DRD4) in this region. DRD4 is a possible risk gene for ADHD, a disorder which often co-occurs with dyslexia.

Chromosome 1 – DYX8

Linkage studies reported a possible locus for dyslexia on chromosome 1p34-1p36 (DYX8, dyslexia susceptibility 8), with strong linkage evidence particularly for the phonological aspects of dyslexia (Rabin et al. 1993; Grigorenko et al. 2001; Tzenova et al. 2004).

Chromosome X – DYX9

Linkage analyses have identified region Xq27 (DYX9, dyslexia susceptibility 9) as correlated with dyslexia based on analyses of an extended Dutch family (de Kovel et al. 2004) and one of the British samples (Fisher et al. 1999).

OTHER REGIONS OF INTEREST

Linkage with developmental dyslexia has also been suggested for other regions. Among others, Igo et al. (2006) reported that a new locus on chromosome 13q12 is linked to group deficits in word reading efficiency (fluency) measures, and Raskind et al. (2005) have presented evidence for phonological decoding efficiency on chromosome 2q22. Based on studies of families with dyslexia and also with ADHD problems, evidence for linkage have been identified in chromosomal regions 14q32, 13q32 and 20q11 (Gayan et al. 2005) and 10q11, 16p12 and 17q22 (Loo et al. 2004).

CONCLUSIONS AND GUIDELINES FOR THE FUTURE

Among the candidate genes discussed above, it is DCDC2 and KIAA0319 that seem to be the most promising. However, even strong linkage evidence for these genes does not allow us to describe them as “genes for reading,” in the sense that the proteins they code would participate directly in the process of learning, or later in reading itself. They rather influence brain development through different processes, such as migration and proliferation of neurons, apoptosis and others. Taking into account the fact that DCDC2 and KIAA0319 only contribute a limited part to the development of dyslexia and that most susceptibility genes are still unknown, it may be possible in the future to identify completely new pathophysiological mechanisms, especially since the expression of candidate genes is not confined only to nervous system tissue. Besides, although the ability to read is typical for the human species, each of the candidate genes is also present in other species. From this point of view it would be interesting to trace how the sequences of candidate genes change in the evolution process in primates, as well as to examine the sequence variability between humans (Fisher & Francks 2006; Schumacher et al. 2007).

Analyses of complex traits, such as dyslexia, often provide false positive or negative results in the process of research. The solution is to verify the obtained results by many independent analyses, but even then it is necessary to bear in mind the fact that neighboring SNPs tend to be co-inherited. Therefore, it is extremely difficult to indicate one specific gene predisposing for dyslexia, and the differentiation between correlation and cause turns out to be the crucial issue (Fisher & Francks 2006). So far no one has succeeded in finding any changes in the structure of the proteins coded by candidate genes which would directly influence dyslexia susceptibility. The observed changes (Tiapale et al. 2003; Francks et al. 2004; Cope et al. 2005a; Hannula-Jouppi et al. 2005) seem to be of minor functional relevance. Indirect evidence for the solution of this problem may be provided by model systems of rodents, or the comparison of the expression level of candidate genes in different regions of human brain (Meng et al. 2005b).

Researchers dealing with the genetic background of developmental dyslexia point out that there is much ambiguity in this subject field (e.g. Fisher & Francks 2006; Schumacher et al. 2007). In the future it seems especially important to:

- identify functional variants in candidate genes predisposing to dyslexia;
- determine the linkage between variability and variations in cognitive dyslectic profiles, including hypothetical cognitive phenotype components, such as orthographic coding, rapid naming and phonological awareness;
- find correlation between genetics and data from structural or functional neuroimaging (for example, whether carriers of putative risk alleles share

common abnormalities in brain development and/or function);

- explore the molecular background of clinically observed comorbidity between symptoms of dyslexia, SSD (speech sound disorder) and other neurodevelopmental disorders, such as ADHD;
- better understand the interaction between genes and the environment in order to identify relevant exogenous risk factors;
- the influence of genotype on the effects of applied therapy and the possibilities of target therapy application.

To sum up, definitive evidence, pointing out which genes are responsible for dyslexia susceptibility, would enable us to achieve a deeper understanding of the genetic background of dyslexia. It will create the possibility for earlier diagnosis and more effective therapy of susceptible children regarding their individual genetic information, subtype of dyslexia and environmental factors. This knowledge will also shed new light on the neurobiology of reading and language cognition. Taking into account the present state of knowledge, we should be careful when offering genetic diagnosis based on the SNPs, STRs, and deletions so far described. It seems clear that there still is not enough evidence to describe reliable predictors of risk for a single individual (Olson 2002; Fisher & Francks 2006).

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