Asian Journal of Psychiatry 30 (2017) 225–229

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Review article

Unfolding the genetic pathways of dyslexia in Asian population: A review

Pawan Sharma[a,*], Rajesh Sagar[b]

[a] Department of Psychiatry, Patan Academy of Health Sciences, Kathmandu, Nepal
[b] Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi, India

ARTICLE INFO

Keywords:
Genetics
Dyslexia
Specific reading disorder
Asia

ABSTRACT

Dyslexia also known as specific reading disorder is a complex heritable disorder with unexpected difficulty in learning to read and spell despite adequate intelligence, education, environment, and normal senses. Over past decades, researchers have attempted to characterize dyslexia neurobiological and genetic levels and unfold its pathophysiology. The genetic research on dyslexia has received attention in Asia from the last decade. Though limited by different constraints the studies from Asia have been able to gather significant evidence in this field. We present a review of studies of genetics in Asian population and suggest future directions.

1. Introduction

Specific reading disorder also known as dyslexia is formally defined by International Dyslexia association (IDA) as a specific learning disability that is neurobiological in origin characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities which typically results from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction (Lyon, 1995). It accounts to 80 to 90% among all learning disorders (Altarac and Saroha, 2007). The life time prevalence of dyslexia in the age group 3 to 17 years of age is 9.7%. Similarly, the prevalence among the children with special health care needs is 28% compared to 5.4% in typically developing children (Altarac and Saroha, 2007). Over past decades, researchers have attempted to characterize dyslexia at cognitive, neurobiological and genetic levels, and have sought to uncover causal pathways between the different levels. The precise underlying biological and cognitive mechanisms of dyslexia are still unclear (Fletcher, 2009). Three converging lines of evidence (family, twin and molecular genetic studies) indicate that dyslexia is highly familial and heritable, but the pathophysiology and mode of transmission are unknown. The clustering of cases in the families, concordance rates in the twins and susceptibility loci in chromosomes strongly suggest the genetic basis of the disorder (Scerri and Schulte-Körne, 2010). Studies have shown that the proportion of variance in reading skills that is explained by genetic endowment is high, with heritability estimates ranging from 0.4 to 0.8. At the same time, it is clear that the genetic architecture underlying dyslexia is complex and multifactorial, involving a combination of polygenecity and heterogeneity (Carrion-Castillo et al., 2013).

At least nine dyslexia susceptibility regions have been mapped and allocated names from DYX1 to DYX9 successively and association studies have identified underlying candidate genes at most of these regions like DYX1C1 (15q 21), DCDC2 and KIAA0319 (6p22.3-p21.3), MRPL19 and C20RF3 (2p16-p15), ROBO1(3p12-q13), KIAA0319L(1p36-p34) (Scerri and Schulte-Körne, 2010). Other candidate genes that have been identified are PCNT, DIP2A, S100B, PRMT2 (Poelmans et al., 2009). Once candidate genes have been identified by genetic association studies, the final step in elucidating the pathway through which they contribute to the disease is the determination of their physiologic function. The disease variant then can be evaluated for how they contribute to the disease susceptibility. In the case of Dyslexia, three genes (DCDC2, KIAA0319, and DYX1C1) appear to influence the migration of developing neurons during early embryogenesis, while ROBO1 appears to affect the extension of axons from neuron cell bodies (Meng et al., 2005; Gibson and Gruen, 2008; Levecque et al., 2009; Hannula-Jouppi et al., 2005).

In modern genetic studies (linkage and association studies) the most common marker used are SNPs (Single Nucleotide Polymorphisms) which are the variations in single bases that occur in the order of one per 100 bases of DNA (Gregory and Gilbert, 2001). SNPs are the most abundant type of genetic marker and their high density makes them ideal for studying the inheritance of genomic regions (Baird et al., 2008). SNPs may be linked to genetic predispositions, frank disorders or adverse drug responses, or they may serve as genetic markers in linkage disequilibrium analysis. The decoding of the human genome and the resulting greater than 3 million single nucleotide polymorphisms (SNPs) present exciting avenues to study the impact of genetic variations on complex phenotypes (Bao et al., 2005). Similarly, in the modern research of dyslexia various copy number variants have been

* Corresponding author.
E-mail address: pawan60@gmail.com (P. Sharma).

http://dx.doi.org/10.1016/j.ajp.2017.06.006
Received 29 April 2017; Received in revised form 31 May 2017; Accepted 6 June 2017

identified. These are structural variation, specifically, a type of duplication or deletion event that affects a considerable number of base pairs (Sharp et al., 2005) and these are identified by using SNPs; associating copy number variations with specific haplotype SNPs by analyzing the linkage disequilibrium (Conrad and Antonarakis, 2007).

Most of the studies in genetics of dyslexia has been done in the children of European and American origin. However, in recent years the research in this field has also been done in children of Asian countries. Among the countries of Asia, the studies are limited to the India and China. We aim at reviewing the studies that have been done in the setting of Asia and discuss about their limitations and future directions. All studies conducted in population of the Asia, which explored the genetics in dyslexia were considered eligible for the present review. The databases of PubMed, Google Scholar and PsycINFO were systematically searched for studies. Search was conducted in April 2017. The search was conducted using different search terms: dyslexia [Title/Abstract] AND genes [Title/Abstract], dyslexia [Title/Abstract] AND "Asia" [All Fields]), reading disorder [Title/Abstract] AND genes [Title/Abstract], reading disorder [Title/Abstract] AND Asia [All Fields], dyslexia [Title/Abstract] AND genetics [Title/Abstract], reading disorder [Title/Abstract] AND genetics [Title/Abstract]. 431 articles were retrieved from the search. English studies were selected for review after reading the abstracts and titles. Among the studies 19 original studies were found and used for review.

The different candidate genes that have been studied in Asian population are shown in Table 1 and individual genes are described below:

1.1. *DYX1C1*

It is the a 78-kb gene located in chromosome 15 region and is first implicated dyslexia candidate following study of a Finnish family transmitting a chromosomal translocation at 15q21 (Bates et al., 2010). The main role of this gene has been implicated in the neuronal migration during the development of neocortex (Wang et al., 2006). A study in India looked at four SNPs corresponding to DYX1C1 candidate gene in 52 dyslexic children and 51 control children of 8–14 years of age using DNA sequencing and found no association of four studied SNPs (Saviour et al., 2008). Similarly, another study studied 6 SNPs corresponding to the DYX1C1 genes in 50 children of reading disorder and 50 control children of the age groups 6- 18 years using DNA sequencing. This study too did not find any significant association with a single SNP (Venkatesh et al., 2011). Similarly, Venkatesh et al. took 210 cases with dyslexia and 256 age-matched controls. Ten single-nucleotide polymorphisms (SNPs) of *DYX1C1* were genotyped in the sample using DNA sequencing. A significant association was observed for the homozygous genotype (GG) of the SNP rs12899331 (3.12%) and individual allele frequency ($P = 0.039$). This study concluded the promoter SNP rs12899331 of DYX1C1 may contribute towards the manifestation of dyslexia (Venkatesh et al., 2014). In a sample of 284 unrelated Chinese children aged 5 to 11 years from Chinese Longitudinal Study of Reading Development were tested for DYX1C1 gene. Significant or marginally significant associations were observed at the marker rs11629841 with children's orthographic judgments especially

Table 1
Studies of genetics of Dyslexia in Asian population.

Study	Sample(n)	Ethnicity	Candidate gene	Results
Chen et al., 2015	502 cases and 522 controls	Chinese	GNPTAB, GNPTG and NAGPA	Positive association (rs17031962 of GNPTAB and rs882294 of NAGPA)
Chen et al., 2014	502 cases and 522 controls	Chinese	DRD2 and SLC6A3	Positive association (rs1079727 of DRD2)
Chen et al., 2017	196 cases and 196 controls	Uyghur Chinese	DCDC2	Positive association (rs807724, rs2274305, and rs4599626)
Kong et al., 2016	409 cases and 410 controls	Chinese	DIP2A	Positive association (rs2255526)
Lim et al., 2014	393 individuals from 131 family	Chinese living in Hong Kong	KIAA0319	No associated Haplotype consisting of rs2760157 and rs807507 associated with phonological awareness
Lim et al., 2011	393 individuals from 131 family	Chinese living in Hong Kong	DYX1C1	Positive association (rs3743205)
Zou et al., 2012a, 2012b	76 cases and 79 controls	Han Chinese	DCDC2	No association
Saviour et al., 2008	50 cases 50 control	Indian	DYX1C1, DCDC2 and KIAA0319	No association
Shao et al., 2015	409 cases 410 controls	Chinese	DYX1C1, DCDC2, KIAA0319, ROBO1, KIAA0319L, and DOCK4	Positive Association (rs28366021 of KIAA0319L, rs4504469 of KIAA0319 and rs2074130 of DOCK4). Odds ratio increased with increasing number of risk alleles
Sun et al., 2014	502 cases and 522 controls	Chinese	DCDC2, KIAA0319	No association
Veerappa et al., 2013	11 families 14 cases and 24 family members	Indian	PCDH11X	Duplications in five cases and a deletion in one case in Xq21.3 region bearing PCDH11X
Venkatesh et al., 2011	52 cases 51 controls	Indian	DYX1C1	No association
Venkatesh et al., 2013	210 cases 256 controls	Indian	DCDC2 KIAA0319	Positive association (rs4504469 of KIAA0319) Negative for DCDC2
Venkatesh et al., 2013	157 cases 212 controls	Indian	MRPL19/C2ORF3, ROBO1 and THEM2	No association
Venkatesh et al., 2014	220 cases 256 controls	Indian	DYX1C1	Positive association (rs1289933)
Wang et al., 2017	288 cases and 343 healthy controls	Chinese	Intergenic variant between *CERBBP* and *ADCY9*	Positive association (rs8049367)
Zhang et al., 2012	284 children	Han Chinese	DYX1C1	Positive association of rs11629841 with orthographic judgment and Chinese character dictation
Zhang et al., 2016	284 children	Han Chinese	DCDC2	Positive association of Minor allele of rs807724 with poor reading performance
Zhao et al., 2016	196 cases 196 controls	Uyghur Chinese	KIAA0319	Positive association (rs6935076 and rs3756821)

processing of specific component of characters and Chinese character dictation. This finding suggested that DYX1C1 influences reading development in the general Chinese population (Zhang et al., 2012). Another study of Chinese population from Hong Kong genotyping eight SNPs from 393 individuals from 131 Chinese families with at least one dyslexic children replicated the previously reported association of rs3743205 of DYX1C1 gene (Lim et al., 2011). Considering the different results, a meta-analysis looking at −3G > A in DYX1C1 gene concluded that this change might not be associated with risk of having reading disorder (Zou et al., 2012a). However, the negative results from other SNPs cannot undermine the role of this gene in pathogenesis of dyslexia

1.2. DCDC2

DCDC2 is expressed in neuronal precursor cells but not in adult neurons. It contains double cortin domains and is expressed in the developing cortex and involved in stabilization and migration of neurons (Meng et al., 2005). It is the most studied candidate gene in genetics of dyslexia. In a study (Chen et al., 2017) of Chinese Uyghur population cluster sampling to recruit a total of 4251 pupils in 28 primary schools was done. After that 196 cases of dyslexia and 196 controls of 8–12 years of were taken and their DNA was isolated from the oral mucosa. Fourteen SNPs were studied using SNPscan method. It was seen that, three SNPs (rs807724, rs2274305, and rs4599626) were associated with dyslexia. rs9467075 and rs2274305 displayed significant associations with dyslexia under the dominant model. rs6456593 and rs6922023 were significantly associated with developmental dyslexia under the dominant model and in the heterozygous genotype. The study also found that the T-G-C-T of the four-marker haplotype (rs9295619-rs807701-rs807724-rs2274305) and the T-A of the two-marker haplotype (rs3765502-1087266) were significantly different between cases and controls. Hence, it was highlighted that DCDC2 gene polymorphisms are associated with developmental dyslexia in Chinese Uyghur children. A high density genotyping in a large unrelated Chinese cohort was done with 502 dyslexic cases and 522 healthy controls. Three (rs2274305, rs4599626, rs9295619) out of 28 studied SNPs of DCDC2 showed nominal association with dyslexia. However, none of these results survived Bonferroni correction for multiple comparisons. Among the nine identified haplotypes study didn't find any risk haplotypes contributing to dyslexia susceptibility (Sun et al., 2014). Similarly, no association was found in the study of children of Indian origin which looked in the four SNPs each of sample sizes of 50 cases and 50 controls (Venkatesh et al., 2011) and 210 cases 256 controls (Venkatesh et al., 2013a) respectively. Analysing data from 284 unrelated children participating in the Chinese Longitudinal Study of Reading Development (CLSRD) showed associations of eight single nucleotide polymorphisms (SNPs) in DCDC2. There was significant support for an association of rs807724 with the intercept for the reading comprehension measure of reading fluency and character reading proving a support that DCDC2 as a risk gene for reading disability (Zhang et al., 2016). Another study (Px et al., 2012) of children of Chinese origin showed no association for two SNPs contradicting the results. From the available literature it can be concluded that not all SNPs of this gene might be associated with dyslexia, however there is no denying the fact that this candidate gene has some role to play in reading and its abberations.

1.3. KIAA0319

This protein is proposed to function in adhesion and attachment and thought to play an important role during neuronal migration in the developing brain. Several single-nucleotide polymorphisms in the promoter region of KIAA0319 shows strong association with multiple reading disability trait (Levecque et al., 2009). A case control study (Venkatesh et al., 2013a) of children in India taking 210 cases and 256 controls have demonstrated the association of dyslexia with SNP rs4504469 of KIAA0319 making this gene an important risk gene. In a similar study (Zhao et al., 2016), 18 single-nucleotide polymorphisms (SNPs) of KIAA0319 in a group of 196 children with dyslexia and 196 controls of Uyghur descent aged 8–12 years; it was seen 7 SNPs of KIAA0319 had nominal significant differences between the cases and controls under specific genotypic models. Two SNPs, rs6935076 and rs3756821, remained significantly associated with dyslexia after Bonferroni correction. Linkage disequilibrium analysis showed three blocks within KIAA0319, and only a 10-SNP haplotype in block 3 to be present at significantly different frequencies in children with dyslexia and controls. This study indicated that genetic polymorphisms of KIAA0319 are associated with an increased risk of dyslexia in the Uyghur population. This gene was also studied in a Chinese cohort with 502 cases of dyslexia and 522 healthy controls. Six SNPs out of 32 (rs69946, rs16889556, rs1091031, rs3903801, rs12193738, rs3756821) had positive association. After logistic regression for age and sex, only rs699463 and rs16889556 showed positive association. However, none of these SNPs remain significant after Bonferroni correction for multiple comparisons (Sun et al., 2014). In another study (Lim et al., 2014) a total of twenty-six SNPs were genotyped from 393 individuals from 131 Chinese families. Analysis for allelic and haplotypic associations was performed and results indicated that KIAA0319 is not associated with Chinese children with dyslexia but a haplotype consisting of rs2760157 and rs807507 SNPs were significantly associated with an onset detection test which is a measure of phonological awareness. This study concluded that KIAA0319 is associated with a reading-related cognitive skill. When we look at the meta-analysis the results are conflicting. An integrated meta-analysis has implicated 931C > T in KIAA0319 could be associated with dyslexia risk (Zou et al., 2012b). A stratified analysis by the study population revealed opposite associations involving KIAA0319 rs4504469 in European and Asian subgroups. The stratified analysis (Shao et al., 2016a) showed that rs9461045 minor allele (T allele) has a protective effect in Asians. This meta-analysis established the effects of specific KIAA0319 polymorphisms vary across populations; analyzing one single nucleotide polymorphism at a time can not fully explain the genetic association for dyslexia. To conclude from the studies, it is clear that this candidate gene is associated with dyslexia in one way or the other.

1.4. Other candidate genes

An Indian study (Venkatesh et al., 2013b) has studied 157 children with dyslexia and 212 normal readers to identify the role of SNPs of four candidate genes namely, MRPL19/C2ORF3, ROBO1 and THEM2. The authors genotyped eight SNPs of these genes using a MassARRAY technique. The study failed to show any association of SNPs and haplotypes of these genes with dyslexia in the Indian population. There is one genome wide scan done in the Indian families where number variations (CNV) scan on 11 dyslexic families consisting of 14 dyslexic subjects and 24 non dyslexic members using 1.8 million combined SNP and CNV marker was done (Veerappa et al., 2013). The authors have found CNVs affecting protocadherin genes in six dyslexics from three families, while none among the non-dyslexic control members showed any CNV in protocadherins. They identified duplications in five cases and a deletion in one case in Xq21.3 region bearing PCDH11X. PCDH11X, expressed in brain is implicated in cell–cell communication, verbal ability, cerebral asymmetry, and dendritic synaptic plasticity, may be regarded as a new candidate gene for dyslexia. A network-based genetic association analysis to investigate associations between six key genes (KIAA0319L, ROBO1, DCDC2, KIAA0319, DOCK4, DYX1C1) in the neuronal migration and neurite outgrowth network and dyslexia risk in a Chinese population was done (Shao et al., 2016b). The authors identified three SNPs, namely rs28366021 of KIAA0319L, rs4504469 of KIAA0319, and rs2074130 of DOCK4, associated with risk of having dyslexia. The classification and regression tree (CART) analysis revealed the prediction value of gene–gene interactions among

rs2074130 of DOCK4, rs4504469 of KIAA0319, rs2274305 of DCDC2, and rs28366021 of KIAA0319L variants and in combination significantly increased dyslexia risk. Few studies in Chinese population has also looked into the candidate genes that have positive association stuttering. In a study (Chen et al., 2015) of unrelated Chinese cohort of 502 dyslexic individuals and 522 healthy controls, 21 SNPs covering the candidate genes GNPTAB, GNPTG and NAGPA were subjected to genotyping. Significant association of rs17031962 in GNPTAB and rs882294 in NAGPA with dyslexia was identified. In the same cohort 23 SNPs covering the two genes DRD2 and SLC6A3 were genotyped. It was seen that rs1079727 in DRD2 showed significant association with developmental dyslexia (Chen et al., 2014). These findings may give credence to the hypothesis that there are common genetic factors underlying the pathophysiology of different speech and language disorders. Kong et al. investigated two genetic variants in DIP2A gene in a Chinese population with 409 cases of dyslexia and 410 healthy controls. It was seen that the risk of dyslexia was significantly increased with rs2255526 G allele and GG genotypes compared with their wild-type counterparts, concluding DIP2A gene could be an associated with dyslexia (Kong et al., 2016). A study in Chinese population (Wang et al., 2017) selected three risk variants of non-syndromic cleft lip with or without cleft palate (NSCL/P) namely rs8049367, rs4791774 and rs2235371, and performed association analysis with 631 elementary school-aged children (288 cases of dyslexia without NSCL/P and 343 healthy controls). After Bonferroni correction for multiple comparisons, the T allele of rs8049367 showed significant association with dyslexia.

2. Discussion

A conclusion can be drawn from the evidence gathered that the relationship between genetic information and dyslexia is not straightforward and there is genetic heterogeneity of dyslexia among populations of Asian origin. There could be different gene–gene interactions between candidate genes as not a single candidate gene can explain the presence of disorder. Such gene–gene interactions have been identified in other complex diseases, such as asthma (Howard et al., 2002) thrombotic stroke (Liu et al., 2009) breast cancer (Ritchie et al., 2001), and pulmonary tuberculosis (Collins et al., 2013). It may be imperative that we look into the interaction of different genes rather than looking into the association studies only. In addition, although dyslexia has been reported to be heritable, environmental influences, such as home schooling, are also considered to contribute to the development of this disorder (Samuelsson and Lundberg, 2003). Though there are no any genome wide association studies published the important role of the association studies on candidate gene cannot be negated (Wilkening et al., 2009). Another important area to see here is the clustering of cases in the Chinese and Indian setting. When we look at the literature world wide the studies have been done in the countries of Europe, North America and Australia. The genes that have been implicated are from association studies, hence the specific cause-effect relationship cannot be established. As seen in the studies above we can see that few candidate genes that are associated with dyslexia are also associated with stuttering (Chen et al., 2015), language impairment (Eicher and Gruen, 2013), ADHD (Plourde et al., 2015) etc. Hence, there could a possibility of overlap with the childhood disorders of language, however, there are no studies that have shown association of these candidate genes with other thought disorders, mood disorders or anxiety disorders. Dyslexia has genetic complexity and the genetic studies are compounded by constraints at the phenotypic level. As there is lack of consensus in physiological, behavioral and cognitive correlates of this disorder delineation of the dyslexia phenotype for genetic studies is further restricted. As a consequence, different diagnostic tools and classification criteria have been used. Similarly, language variation has led to variation in operational definitions of yielding increased heterogeneity. This arises many questions when trying to interpret and integrate data from multiple studies. Hence, the phenotype selection could create bias in the results. To cite an example subjects that have 'phonological coding dyslexia' in one study sample might not be directly comparable to those reported to have 'spelling disability' or 'reading/writing disability in spite all the problems being qualified for having dyslexia (Fisher and DeFries, 2002).

There are multiple limitations of the data presented from Asian countries. The most important limitation of data collected here is the non- generalizability considering the lack of inclusion of all ethnic groups. The selection of SNPs in most of the studies are based on a previous study, and the whole studies are devoted in determining whether these polymorphisms show the same associations in dyslexia of Asian children which may not provide a comprehensive picture of the total genetic variability in this population. Most of the studies have looked into the predefined SNPs and tried to replicate the findings from the studies of western world. Another important limitation is of sample size. The sample size taken in most of the studies is of moderate to small and doesn't meet the standard criteria required (Hong and Park, 2012).

Considering the limitations future studies should consider the role of gene-environment interactions in the development of developmental dyslexia as well. Hence, a genome wide association study is mandatory. From the studies above it is clear that the research has mainly be conducted in Indian and Chinese setting. The studies need to see genetics of children of other ethnic groups of Asia to understand the modes of heritability in our setting. There is a large amount of data that needs to be accumulated and integrated in order to reach a coherent understanding that will enable us to disentangle the environmental and genetic effects on dyslexia. Apart from this there is a prospect of integrating neuroimaging data with genetic and neurobehavioral data to gain a mechanistic model of gene, brain function and structure, and ultimate behavioral phenotype (Eicher and Gruen, 2013). The imaging-genetic studies of dyslexia although a new field, would be helpful in unlocking new insights behind the mechanisms and pathophysiology underlying dyslexia.

References

Altarac, M., Saroha, E., 2007. Lifetime prevalence of learning disability among US children. Pediatrics 119 (Suppl), S77–S83.

Baird, N.A., Etter, P.D., Atwood, T.S., Currey, M.C., Shiver, A.L., Lewis, Z.A., Johnson, E.A., 2008. Rapid SNP discovery and genetic mapping using sequenced RAD markers. PLoS One 3 (10), e3376.

Bao, Y.P., Huber, M., Wei, T.-F., Marla, S.S., Storhoff, J.J., Müller, U.R., 2005. SNP identification in unamplified human genomic DNA with gold nanoparticle probes. Nucleic Acids Res. 33 (2) e15–e15.

Bates, T.C., Lind, P.A., Luciano, M., Montgomery, G.W., Martin, N.G., Wright, M.J., 2010. Dyslexia and DYX1C1: deficits in reading and spelling associated with a missense mutation. Mol. Psychiatry 15 (12), 1190–1196.

Carrion-Castillo, A., Franke, B., Fisher, S.E., 2013. Molecular genetics of dyslexia: an overview. Dyslexia (Chichester, England) 19 (4), 214–240.

Chen, H., Wang, G., Xia, J., Zhou, Y., Gao, Y., Xu, J., Sun, Y., 2014. Stuttering candidate genes DRD2 but not SLC6A3 is associated with developmental dyslexia in Chinese population. Behav. Brain Funct. BBF 10, 29.

Chen, H., Xu, J., Zhou, Y., Gao, Y., Wang, G., Xia, J., Sun, Y., 2015. Association study of stuttering candidate genes GNPTAB, GNPTG and NAGPA with dyslexia in Chinese population. BMC Genet. 16.

Chen, Y., Zhao, H., Zhang, Y., Zuo, P., 2017. DCDC2 gene polymorphisms are associated with developmental dyslexia in Chinese Uyghur children. Neural Regener. Res. 12 (2) 259–266.

Collins, R.L., Hu, T., Wejse, C., Sirugo, G., Williams, S.M., Moore, J.H., 2013. Multifactor dimensionality reduction reveals a three-locus epistatic interaction associated with susceptibility to pulmonary tuberculosis. BioData Mining 6 (1), 4.

Conrad, B., Antonarakis, S.E., 2007. Gene duplication: a drive for phenotypic diversity and cause of human disease. Annu. Rev. Genomics Hum. Genet. 8, 17–35.

Eicher, J.D., Gruen, J.R., 2013. Imaging-genetics in dyslexia: connecting risk genetic variants to brain neuroimaging and ultimately to reading impairments. Mol. Genet. Metab. 110 (3), 201–212.

Fisher, S.E., DeFries, J.C., 2002. Developmental dyslexia: genetic dissection of a complex cognitive trait. Nat. Rev. Neurosci. 3 (10), 767–780.

Fletcher, J.M., 2009. Dyslexia: the evolution of a scientific concept. J. Int. Neuropsychol. Soc. JINS 15 (4), 501–508.

Gibson, C.J., Gruen, J.R., 2008. The human lexinome: genes of language and reading. J. Commun. Disord. 41 (5), 409–420.

Gregory, S., Gilbert, J., 2001. Strategies for genotype generation. Current Protocols in Human Genetics. John Wiley Sons, Inc.

Hannula-Jouppi, K., Kaminen-Ahola, N., Taipale, M., Eklund, R., Nopola-Hemmi, J.,

Kääriäinen, H., Kere, J., 2005. The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. PLoS Genet. 1 (4), e50.
Hong, E.P., Park, J.W., 2012. Sample size and statistical power calculation in genetic association studies. Genom. Inf. 10 (2), 117–122.
Howard, T.D., Koppelman, G.H., Xu, J., Zheng, S.L., Postma, D.S., Meyers, D.A., Bleecker, E.R., 2002. Gene–gene interaction in asthma: IL4RA and IL13 in a dutch population with asthma. Am. J. Hum. Genet. 70 (1), 230–236.
Kong, R., Shao, S., Wang, J., Zhang, X., Guo, S., Zou, L., Song, R., 2016. Genetic variant in DIP2A gene is associated with developmental dyslexia in Chinese population. Am. J. Med. Genet. B 171B (2), 203–208.
Levecque, C., Velayos-Baeza, A., Holloway, Z.G., Monaco, A.P., 2009. The dyslexia-associated protein KIAA0319 interacts with adaptor protein 2 and follows the classical clathrin-mediated endocytosis pathway. Am. J. Physiol. Cell Physiol. 297 (1), C160–C168.
Lim, C.K.P., Ho, C.S.H., Chou, C.H.N., Waye, M.M.Y., 2011. Association of the rs3743205 variant of DYX1C1 with dyslexia in Chinese children. Behav. Brain Funct. 7, 16.
Lim, C.K.-P., Wong, A.M.-B., Ho, C.S.-H., Waye, M.M.-Y., 2014. A common haplotype of KIAA0319 contributes to the phonological awareness skill in Chinese children. Behav. Brain Funct. BBF 10, 23.
Liu, J., Sun, K., Bai, Y., Zhang, W., Wang, X., Wang, Y., Hui, R., 2009. Association of three-gene interaction among MTHFR, ALOX5AP and NOTCH3 with thrombotic stroke: a multicenter case-control study. Hum. Genet. 125 (5–6), 649–656.
Lyon, G.R., 1995. Toward a definition of dyslexia. Ann. Dyslexia 45 (1), 1–27.
Meng, H., Smith, S.D., Hager, K., Held, M., Liu, J., Olson, R.K., Gruen, J.R., 2005. DCDC2 is associated with reading disability and modulates neuronal development in the brain. Proc. Natl. Acad. Sci. U. S. A. 102 (47), 17053–17058.
Plourde, V., Boivin, M., Forget-Dubois, N., Brendgen, M., Vitaro, F., Marino, C., Dionne, G., 2015. Phenotypic and genetic associations between reading comprehension, decoding skills, and ADHD dimensions: evidence from two population-based studies. J. Child Psychol. Psychiatry Allied Discipl. 56 (10), 1074–1082.
Poelmans, G., Engelen, J.J.M., Van Lent-Albrechts, J., Smeets, H.J., Schoenmakers, E., Franke, B., Schrander-Stumpel, C., 2009. Identification of novel dyslexia candidate genes through the analysis of a chromosomal deletion. Am. J. Med. Genet. B 150B (1), 140–147.
Ritchie, M.D., Hahn, L.W., Roodi, N., Bailey, L.R., Dupont, W.D., Parl, F.F., Moore, J.H., 2001. Multifactor-dimensionality reduction reveals high-order interactions among estrogen-Metabolism genes in sporadic breast cancer. Am. J. Hum. Genet. 69 (1), 138–147.
Samuelsson, S., Lundberg, I., 2003. The impact of environmental factors on components of reading and dyslexia. Ann. Dyslexia.
Saviour, P., Kumar, S., Kiran, U., Ravuri, R.R., Rao, V.R., Ramachandra, N.B., 2008. Allelic variants of DYX1C1 are not associated with dyslexia in India. Indian J. Hum. Genet. 14 (3), 99–102.
Scerri, T.S., Schulte-Körne, G., 2010. Genetics of developmental dyslexia. Eur. Child Adolesc. Psychiatry 19 (3), 179–197.
Shao, S., Niu, Y., Zhang, X., Kong, R., Wang, J., Liu, L., Song, R., 2016a. Opposite associations between individual KIAA0319 polymorphisms and developmental dyslexia risk across populations: a stratified meta-analysis by the study population. Sci. Rep. 6.
Shao, S., Kong, R., Zou, L., Zhong, R., Lou, J., Zhou, J., Song, R., 2016b. The roles of genes in the neuronal migration and neurite outgrowth network in developmental dyslexia: single- and multiple-risk genetic variants. Mol. Neurobiol. 53 (6), 3967–3975.
Sharp, A.J., Locke, D.P., McGrath, S.D., Cheng, Z., Bailey, J.A., Vallente, R.U., Eichler, E.E., 2005. Segmental duplications and copy-number variation in the human genome. Am. J. Hum. Genet. 77 (1), 78–88.
Sun, Y., Gao, Y., Zhou, Y., Chen, H., Wang, G., Xu, J., Tan, L.H., 2014. Association study of developmental dyslexia candidate genes DCDC2 and KIAA0319 in Chinese population. Am. J. Med. Genet. B 165B (8), 627–634.
Veerappa, A.M., Saldanha, M., Padakannaya, P., Ramachandra, N.B., 2013. Genome-wide copy number scan identifies disruption of PCDH11X in developmental dyslexia. Am. J. Med. Genet. B 162 (8), 889–897.
Venkatesh, S.K., Siddaiah, A., Padakannaya, P., Ramachandra, N.B., 2011. An examination of candidate gene SNPs for dyslexia in an indian sample. Behav. Genet. 41 (1), 105–109.
Venkatesh, S.K., Siddaiah, A., Padakannaya, P., Ramachandra, N.B., 2013a. Analysis of genetic variants of dyslexia candidate genes KIAA0319 and DCDC2 in Indian population. J. Hum. Genet. 58 (8), 531–538.
Venkatesh, S.K., Siddaiah, A., Padakannaya, P., Ramachandra, N.B., 2013b. Lack of association between genetic polymorphisms in ROBO1, MRPL19/C2ORF3 and THEM2 with Developmental Dyslexia. Gene 529 (2), 215–219.
Venkatesh, S.K., Siddaiah, A., Padakannaya, P., Ramachandra, N.B., 2014. Association of SNPs of DYX1C1 with developmental dyslexia in an Indian population. Psychiatr. Genet. 24 (1), 10–20.
Wang, Y., Paramasivam, M., Thomas, A., Bai, J., Kaminen-Ahola, N., Kere, J., Loturco, J.J., 2006. DYX1C1 functions in neuronal migration in developing neocortex. Neuroscience 143 (2), 515–522.
Wang, B., Zhou, Y., Leng, S., Zheng, L., Lv, H., Wang, F., Sun, Y., 2017. Genetic polymorphism of nonsyndromic cleft lip with or without cleft palate is associated with developmental dyslexia in Chinese school-aged populations. J. Hum. Genet. 62 (2), 265–268.
Wilkening, S., Chen, B., Bermejo, J.L., Canzian, F., 2009. Is there still a need for candidate gene approaches in the era of genome-wide association studies? Genomics 93 (5), 415–419.
Zhang, Y., Li, J., Tardif, T., Burmeister, M., Villafuerte, S.M., McBride-Chang, C., Shu, H., 2012. Association of the DYX1C1 dyslexia susceptibility gene with orthography in the chinese population. PLoS One 7 (9), e42969.
Zhang, Y., Li, J., Song, S., Tardif, T., Burmeister, M., Villafuerte, S.M., Shu, H., 2016. Association of DCDC2 polymorphisms with normal variations in reading abilities in a Chinese population. PLoS One 11 (4).
Zhao, H., Chen, Y., Zhang, B., Zuo, P., 2016. KIAA0319 gene polymorphisms are associated with developmental dyslexia in Chinese Uyghur children. J. Hum. Genet. 61 (8) 745–752.
Zou, L., Chen, W., Shao, S., Sun, Z., Zhong, R., Shi, J., Song, R., 2012a. Genetic variant in KIAA0319, but not in DYX1C1, is associated with risk of dyslexia: an integrated meta-analysis. Am. J. Med. Genet. B 159B (8), 970–976.
Zou, P.X., Wu, H.R., Li, Z.C., Cao, X.D., Pang, L.J., Yang, L., Liu, F., Zhao, F., 2012b. Association of polymorphisms in the DCDC2 gene with developmental dyslexia in the Han Chinese. Chin. Med. J. (Engl.) 125 (4), 622–625.