Title: Study of KIAA0319, DYXIC1 and DCDC2 Gene Polymorphisms in Children with Dyslexia in Indian Population

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Abstract:

Background:

Dyslexia is a typical learning disability that does not affect intelligence but causes problems with reading, writing, and spelling. It is influenced by certain genes, due to which several researchers have attempted to identify the susceptible gene. Dyslexia is incurable and diagnosis is difficult because it always overlaps with other learning disabilities. Hence, timely assessment and intervention consequently give the best results. Therefore, our aim was to find the relation between dyslexia and single nucleotide polymorphisms (SNPs) in several candidate genes like DYX1C1, KIAA0319, and DCDC2 in Indian population.

Methods:

In the present study, 103 individuals with dyslexia and 100 controls in the age group between 6 to 15 years were taken. Thirteen SNPs in the *KIAA* gene, seven SNPs of DCDC2, and three SNPs of the DYX1C1 gene were analysed by the Mass Array technique.

Results:

The association of dyslexia with SNPs *rs*3756821, *rs*6935076, *rs*4576240 of the KIAA gene was found significant. A significant association was found with rs600753 of the DYX1C1 gene and dyslexia and we could not find any association of the DCDC2 gene with dyslexia.

Conclusions:

Prerequisite genetic analysis is necessary for the diagnosis of dyslexia as it is a crucial educational barrier. Treatment is known to be most effective if dyslexia is identified in the early stages for effective intervention for children before they experience prolonged reading failure. Further, it helps in prenatal diagnosis for early intervention.

Keywords: Dyslexia, DCDC2, DYX1C1, KIAA gene, SNP

Highlights:

- Dyslexia is a neurological condition characterized by difficulty in reading due to inappropriate word decoding which has a strong genetic basis.
- Several candidate genes are thought to be associated with dyslexia and very few studies are done to identify the genes that are ethnic in the dyslexic population.
- Our study is the second study in the Indian population and first in the Telangana population to check the association of candidate genes in dyslexic children.
- These candidate genes can be used as a diagnostic marker for early detection and early remedial measures can be taken.
- Prenatal diagnosis can also be done for early intervention.

Introduction:

Dyslexia is a neurological condition characterized by difficulty in reading due to inappropriate word decoding in absence of overt neurological deficits (Shidhani & Arora 2012, Mascheretti et al, 2017). It has a strong genetic basis and most commonly seen in children (Meng et al, 2005). A common criterion for the diagnosis of dyslexia is reading accuracy below the mean by more than 1.5 SD, which is approximately 7% of the population identified as dyslexic (Peterson RL & Pennington BF 2012).

The global incidence of dyslexia is about 5-20%, whereas, in India, the incidence is about 10-15% (Mogasale et al, 2012). Moreover, it accounts for 80% of learning disabilities with males affected more than females. This is due to fetal testosterone levels during late pregnancy (Miller & Halpern, 2014, Hines, 2011).

Multiple theories were postulated to explain the etiology of dyslexia, but the exact cause is still not known (kere, 2014, Fletcher & Miciak, 2017, Ring & Black 2018, Snowling, Hulme & Nation, 2020, Gialluisi et al, 2020). Sixty percent (60%) of the disorder is due to genetic component (Schulte-Körne, 2010). Several candidate genes are thought to be associated with dyslexia which includes DYX1C1 on 15q21 (Lim Cadmon et al 2011), ROBO1 on 3p12 (Tran et al, 2014, Mascheretti et al, 2020), DCDC2 (Burbridge et al 2008), KIAA0319 on 6p22 (Francks et al, 2004), GRIN2B (Ludwig et al, 2010), KIAA0319L of DYX8 locus (Platt et al, 2013), MRPL19 and C2ORF3 on 2p12 (Anthoni et al, 2007, Newbury 2011). Many of these genes have been proved to be connected in neuronal development of brain. In specific, researchers suggest DYX1C1, DCDC2, and KIAA0319 play an important role during the growth of the rat cortex (De Kovel et al, 2008, Carrion, Franke, & Fisher, 2013).

In two Finnish families, DYX1C1 was the primary gene identified through a chromosomal translocation that generated a breakpoint at the DYX1C1 locus 9 (Nopola-Hemmi et al, 2002). The same group of research scholars has done a further assessment and found disruption of the DYX1C1 gene in all affected members with dyslexia (Taipale et al, 2003). However, some other articles have failed to show the interconnection between DYX1C1 gene and dyslexia in their population (Bellini et al, 2005).

Luciano group (2007) demonstrated that the first 4 exons of the KIAA0319 gene was associated with dyslexia. Evidence for the association of SNPs of KIAA0319 and DCDC2 was obtained by the studies in the USA (Francks et al 2004), UK (Scerri et al, 2011), and German populations (Neef et al, 2017). Allessandro Gialluisi. (2019) et al has done genome wide association scan and identified novel genes linked with dyslexia.

The present study aims to find the link between dyslexia and single nucleotide polymorphisms (SNPs) in several candidate genes like DYX1C1, KIAA0319, and DCDC2 in Telangana population of India.

Materials and methods:

Study subjects:

Study participants comprised of 203 subjects who were selected from Niloufer Hospital (Telangana) and Dyslexia Association of Telangana, Naryanaguda, Hyderabad. Our study was approved by the ethical committee of the Institute of Genetics and Hospital for Genetic Diseases. With the help of psychiatrists and psychologists, 103 cases who were confirmed with dyslexia and 100 apparently healthy control samples were selected for the study. Both cases and controls were matched with age and gender.

A total of three SNPs for DYX1C1 (rs16976354, rs600753, rs17819126), seven SNPs for DCDC2 (rs1091047, rs1419228, rs2274305, rs33914824, rs6922023, rs9467075, rs9467076) and 13 SNPs for KIAA0319 gene (rs2744559, rs28501680, rs2744550, rs6935076, rs8075434, rs9467247, rs10946705, rs807541, rs3212236, rs4576240, rs9461045, rs807535 and rs3756821) were evaluated in this study.

Inclusion criteria:

Dyslexic subjects aged between 6-15 years with an IQ of more than 90 and a discrepancy between ability and achievements were included in the study.

Exclusion criteria:

Subjects with acquired dyslexia, speech sound disorder (SSD), mental retardation due to birth trauma, infections like meningitis and encephalitis were excluded from the study.

Controls:

Apparently healthy children aged 6 to 15 years without learning difficulties were recruited from the Niloufer Hospital, Hyderabad, Telangana.

Genotyping:

Four milliliters of blood was collected in EDTA tube from each individual. DNA was extracted by QIAamp DNA Blood Mini Kit and its purity is checked by ND-Spectrophotometer. Genotyping was performed using iPLEX Gold chemistry. Polymerase chain reaction and Mass extend primers for multiplexed assays were designed automatically by the Mass Array Designer software.

Statistical analysis:

Phenotypic and genotypic data were analyzed using SPSS software, version 16.0. One-way ANOVA and Logistic regression was done for estimation of allele frequencies. The association analysis was carried using the Chi-square test and odds ratio. Haploview software was used for linkage disequilibrium (LD) analysis of SNPs and haplotype selection.

Results:

203 participants (103 cases and 100 control) were recruited for the present study. All were genotyped successfully. Among the cases, 68 (66.01%) were males and 35 (33.99%) were females ($p < 0.0001$).

Hardy-Weinberg Equilibrium:

All the SNPs in this study followed the Hardy Weinberg equilibrium (p-value < 0.001) (Fig 1 and 2). Figure 1 indicates scattered plots exploring the relationship between genotype frequencies of f_{AA} versus f_{AB} and f_{AA} versus f_{BB}. It was observed that the SNPs fall closely around the HWE curve (blue line).

Figure 2 is a ternary plot which represents genotype frequencies, allele frequencies, and infer the equilibrium status of a genetic marker. It was observed that all the SNPs were located within the acceptance region around parabolas which represent the HW equation (p-value < 0.001).

Allele frequencies

SNPs with MAF > 0.01(minor allele frequency) were considered for further analysis. MAF = 0 value represents the presence of only one allele in the entire set of samples. There were 18 SNPs

with MAF > 0.01. However, five SNPs (rs10946705, rs16976354, rs2744550, rs2744559 and rs28501680) with MAF < 0.01 were removed from further analysis (Table 1).

Allelic association was observed in the present study for the SNP rs600753 in DYX1C1 gene (p = 0.013) and for the SNPs rs3756821, rs4576240, rs6935076 in KIAA0319 gene (p = 0.001, 0.0133 and 0.003 respectively) as represented in Table 2.

Genotypic distribution:

In the present study, there was a significant genotypic association between dyslexia cases and controls for the SNPs rs3756821 (Table 3). Moreover, three haplotype blocks were also identified (Figure 3) indicating that the SNPs rs6935076 & rs3756821 of the KIAA0319 gene are linked together.

Discussion:

Dyslexia is a vital educational obstacle and an invisible handicap (Leseyane et al, 2018). Detailed genetic research is required to identify the genes that are responsible for dyslexia in the ethnic population which imparts simple diagnostic aids to detect this disorder and aids clinicians for early diagnosis of dyslexia.

In the present study, we found male predominance in the dyslexia cases. This may be due to the effect of male hormones (fetal testosterone) on the nervous system during the pre or perinatal period. This could also be the reason that boys are frequently seen to be affected more than girls. (Miller & Halpern, 2014, Hines, 2011). In India, this may be due to male children visiting more to hospital compared to females. The higher incidence of dyslexia among boys than girls in few studied done earlier demonstrate that it may be due to gender bias or may be due to an artefact of the participation selection process (Seigel & Smythe, 2005, Share & Silva, 2003). However, a

study done by Liederman, Kantrowitz and Flannery (2005) demonstrated that male vulnerability is not due to bias. In contrast, other study found no significant gender related differences (Jiménez et al, 2011).

Among the 13 SNPs from KIAA0319 gene, significant association was found only with SNPs rs 3756821 ($p= 0.001$), rs69350760 ($p= 0.003$) and rs4576240 ($p= 0.01$) of KIAA gene and dyslexia. To our knowledge, this is the first study to show a significant association of KIAA0319 in dyslexia in the Telangana population. Our results were consistent with those of a study by Zhao et al (2016) that provided a proof for an association of rs6935076 and rs3756821 with dyslexic individuals in the Chinese population. However, venkatesh et al (2013) did not find an association of rs4576240 and dyslexia in the Indian population. Several studies have shown that the KIAA gene codes a plasma membrane protein which is involved in the regulation of neuronal migration (Paracchini et al, 2006, Velayos-Baeza et al, 2008, Levecque et al, 2009). The reading disability might be due to neuronal migration irregularities, and downregulation of the KIAA0319 gene. This provides a link between the KIAA0319 gene and dyslexia.

In the present study, we analyzed three SNPs from the DYX1C1 gene but could only find significant association with rs600753 of the DYX1C1 gene and dyslexia ($p < 0.01$). Dahdouh et al (2009) first reported the gender-specific association of rs600753 with dyslexia. Muller et al (2018) observed that rs600753 is connected with dyslexia-specific differential allelic expression of DYX1C1. Other previous studies suggested that DYX1C1 is involved in the regulation of estrogen receptors (ER1 and ER2), and may thus affect brain development and regulate cognitive functions (Massinen et al, 2009). Therefore, DYX1C1 might be linked with ERs and neuronal migration in causing dyslexia.

Chen et al. (2017) observed that DCDC2 gene polymorphisms (rs2274305) were associated with dyslexia. In the present study we tried to reproduce this finding but we could not find any association of this polymorphism with dyslexic individuals in Indian population ($p = 0.1$). However, the results of our study are consistent with the results of the studies done by Venkatesh et al,(2013, 2014) who showed the link between dyslexia and SNP rs4504469 of KIAA0319, SNP rs12899331 of DYX1C1 and not with any SNPs of DCDC2 in Indian population.

This is the first study in India to show that the significant SNPs rs6935076, rs3756821 of the KIAA0319 gene are linked together as represented in Figure 3.

SNPs do not change through generations and are inherited. Hence, analysis of SNPs is an important step. Besides, this may also be useful for developing diagnostic, therapeutic, and preventative strategies.

Conclusion:

The present study is the first one to associate three genes (DYX1C1, KIAA0319, and DCDC2) in 103 patients with dyslexia in the Telangana population and second study in Indian population. A statistically significant association with SNPs of KIAA and the DYX1C1 gene was observed in this study. Recognizing such susceptible genes will aid in understanding the relationships between specific cognitive deficits contributing to poor reading. Moreover, genetic studies can provide crucial breakthroughs in knowing the biology of complex cognition in dyslexic individuals.

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Fig 1: Scatter plots to explore the relationship between genotype frequencies of f_{AA} versus f_{AB} and f_{AA} versus f_{BB}.

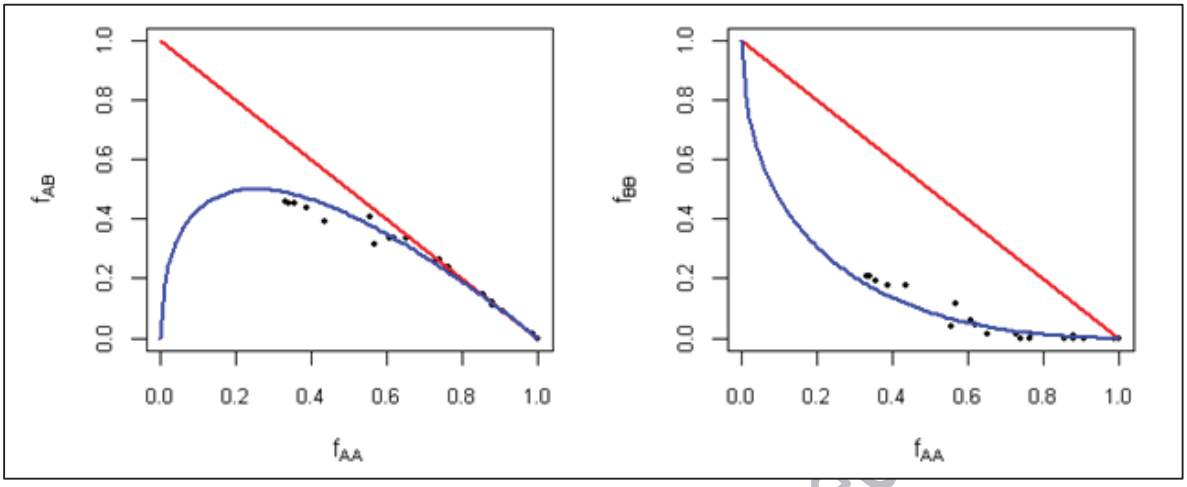


Fig 2: Ternary plot

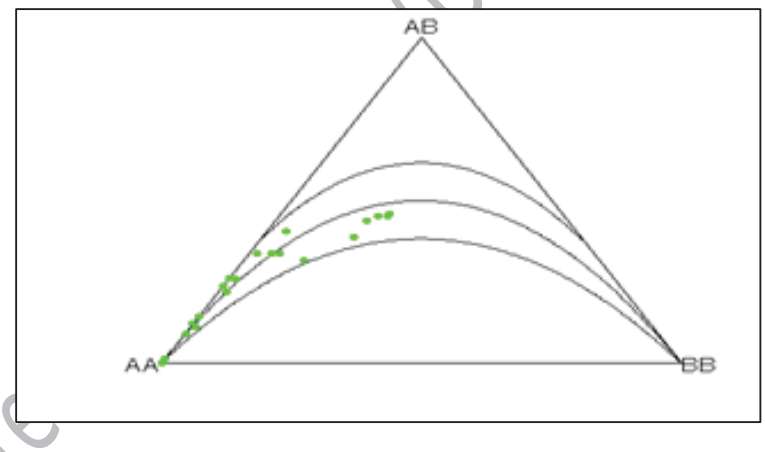


Table 1: The frequency of minor allele calculated from the samples

SNP	GENES	A1	A2	MAF	NCHROBS	Chromosome	Chromo-position	aa_change
rs16976354	DYX1C	0	G	0	410	Chr15	55790414	38
rs17819126	DYX1C	T	C	0.06098	410	Chr15	55789910	271
rs600753	DYX1C	T	C	0.3707	410	Chr15	55759193	191
rs1091047	DCDC2	C	G	0.1317	410	Chr6	24295256	
rs1419228	DCDC2	G	A	0.1244	410	Chr6	24178306	
rs2274305	DCDC2	A	G	0.3951	410	Chr6	24291203	221
rs33914824	DCDC2	G	C	0.06098	410	Chr6	24302046	152
rs6922023	DCDC2	A	G	0.1829	410	Chr6	24348117	
rs9467075	DCDC2	A	G	0.1439	410	Chr6	24205236	339
rs9467076	DCDC2	C	T	0.1195	410	Chr6	24209255	
rs10946705	KIAA0319	G	C	0.007538	398	Chr6	24556936	910
rs2744550	KIAA0319	0	T	0	410	Chr6	24576631	558
rs2744559	KIAA0319	0	C	0	410	Chr6	24576631	522
rs28501680	KIAA0319	0	G	0	410			
rs3212236	KIAA0319	G	A	0.4366	410	Chr6	24648455	
rs4576240	KIAA0319	T	G	0.04634	410	Chr6	24596472	133
rs6935076	KIAA0319	T	C	0.2268	410	Chr6	24644322	

rs807534	KIAA0319	C	T	0.06585	410	Chr6	24551664	1004
rs807535	KIAA0319	C	T	0.07317	410	Chr6	24551729	982
rs807541	KIAA0319	C	T	0.2415	410	Chr6	24559281	889
rs9461045	KIAA0319	T	C	0.439	410	Chr6	24649061	
rs9467247	KIAA0319	A	C	0.4171	410	Chr6	26467219	
rs3756821	KIAA0319	A	G	0.2756	410	chr6	24646821	

A1=Minor allele, A2=Major allele, MAF=Minor Allele Frequency, NCHROBS=Non-missing allele count.

Table 2: Allelic association between patients with dyslexia and controls

Genes	SNP	A1	F_A	F_U	A2	OR	95 % CI	p value	FDR_BH
DYX1C1	rs17819126	T	0.0714	0.05	C	1.46	0.64 – 3.33	0.36	0.6301
DYX1C1	rs600753	T	0.4286	0.31	C	1.66	1.11 – 2.50	0.01	0.0631*
DCDC2	rs1091047	C	0.1286	0.135	G	0.94	0.53 – 1.67	0.84	0.9066
DCDC2	rs1419228	G	0.1143	0.135	A	0.82	0.45 – 1.48	0.52	0.8317
DCDC2	rs2274305	A	0.3571	0.435	G	0.72	0.48 – 1.07	0.10	0.3249
DCDC2	rs33914824	G	0.0714	0.05	C	1.46	0.64 – 3.33	0.36	0.6301
DCDC2	rs6922023	A	0.2143	0.15	G	1.54	0.92 – 2.57	0.09	0.3249
DCDC2	rs9467075	A	0.1286	0.16	G	0.77	0.44 – 1.34	0.36	0.6301
DCDC2	rs9467076	C	0.1143	0.125	T	0.90	0.49 – 1.64	0.73	0.9066
KIAA0319	rs3212236	G	0.4429	0.43	A	1.05	0.71 – 1.55	0.79	0.9066
KIAA0319	**rs3756821**	A	0.3429	0.205	G	2.02	1.29 – 3.16	0.001 *	0.03353
KIAA0319	**rs4576240**	T	0.0714	0.02	G	3.76	1.22 – 11.56	0.01*	0.0631

KIAA0319	rs6935076	T	0.2857	0.165	C	2.02	1.25 – 3.26	0.003 *	0.03353
KIAA0319	rs807534	C	0.0714	0.06	T	1.20	0.54 – 2.64	0.64	0.9066
KIAA0319	rs807535	C	0.0714	0.075	T	0.94	0.45 – 1.99	0.88	0.9066
KIAA0319	rs807541	C	0.2143	0.27	T	0.73	0.46 – 1.16	0.18	0.4456
KIAA0319	rs9461045	T	0.4429	0.435	C	1.03	0.69 – 1.52	0.87	0.9066
KIAA0319	rs9467247	A	0.2429	0.18	T	1.461	0.90-2.35	0.1197	0.3249

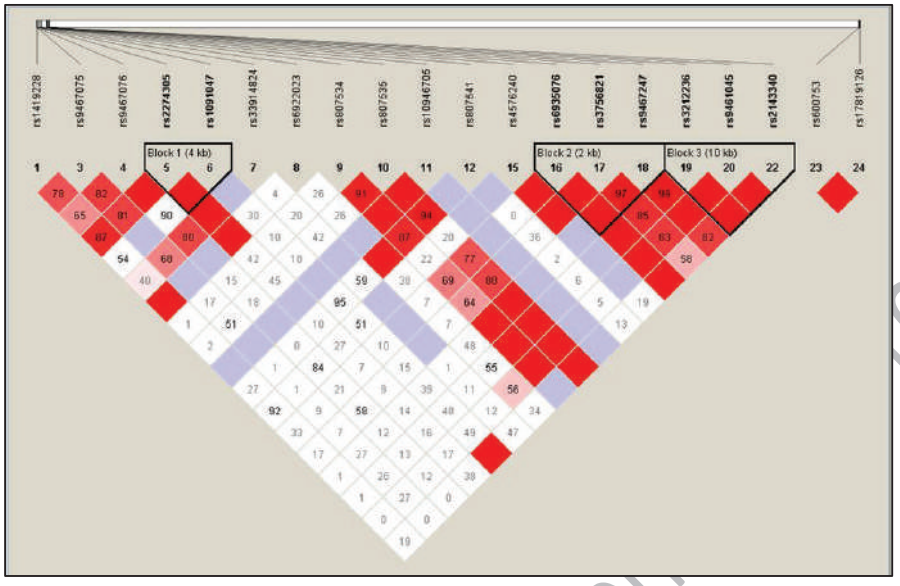
A1: Minor allele name (based on the whole sample); F_A: Frequency of minor allele in cases; F_U: Frequency of minor allele in controls; A2: Major allele name; OR: Estimated odds ratio; CI: Confidence Interval; FDR_BH: Benjamini & Hochberg FDR Corrected p-values. *P< 0.05 is considered as significant.

Table 3: The genotypic distribution between patients with dyslexia and controls

SNP	A1	A2	TEST	CASES	CONTROLS	p value	FDR_BH
rs1091047	C	G	GENO	0/27/78	0/27/73	NA	NA
rs1419228	G	A	GENO	3/18/84	0/27/73	NA	NA
rs17819126	T	C	GENO	0/15/90	0/10/90	NA	NA
rs2143340	C	T	GENO	9/33/63	0/36/64	NA	NA
rs2274305	A	G	GENO	18/39/48	18/51/31	0.07	0.15312
rs3212236	G	A	GENO	24/45/36	19/48/33	0.70	0.7602
rs33914824	G	C	GENO	0/15/90	0/10/90	NA	NA
rs3756821	A	G	GENO	18/36/51	6/29/65	0.015	0.09336
rs4576240	T	G	GENO	0/15/90	0/4/96	NA	NA
rs600753	T	C	GENO	24/42/39	12/38/50	0.06	0.15312
rs6922023	A	G	GENO	3/39/63	0/30/70	NA	NA
rs6935076	T	C	GENO	12/36/57	0/33/67	NA	NA
rs807534	C	T	GENO	0/15/90	2/8/90	NA	NA
rs807535	C	T	GENO	0/15/90	0/15/85	NA	NA
rs807541	C	T	GENO	3/39/63	5/44/51	NA	NA
rs9461045	T	C	GENO	24/45/36	19/49/32	0.64	0.7602
rs9467075	A	G	GENO	3/21/81	0/32/68	NA	NA
rs9467076	C	T	GENO	0/24/81	0/25/75	NA	NA
rs9467247	A	C	GENO	21/45/39	18/48/34	0.76	0.7602

SNP: single nucleotide polymorphism, GENO:Genotype , Cases :Dyslexic cases, NA: Not applicable A1: Minor allele name (based on the whole sample); A2: Major allele name; CHISQ: Basic allelic test chi-square (1df); P:p-value of chi-square test; FDR_BH: Benjamini & Hochberg FDR Corrected p-values. P< 0.05 is considered significant

Fig 3: Linkage disequilibrium between the markers



Red color indicates high co-relation