

The KIAA0319 Gene Polymorphisms are Associated with Developmental Dyslexia in Chinese Uyghur Children

Association of KIAA0319 Polymorphisms with Developmental Dyslexia

Hua Zhao*, Yun Chen*, Bao-ping Zhang*, Peng-xiang Zuo*¹

Department of Medical School, University of Shihezi, Xinjiang, China, 832002

ABSTRACT To investigate the association of KIAA0319 gene polymorphisms and developmental dyslexia in individuals of Uyghurian descent. Eighteen single nucleotide polymorphisms (SNP) of gene KIAA0319 were screened in a group of 196 patients with dyslexia and 196 controls of Uyghur descent by determined the genotypes using a custom-by-design 48-Plex SNPscan™ Kit. SAS 9.1.3 software were used for data analysis. Seven SNPs ($P_{\min}=0.001$) of KIAA0319 have significant differences between the cases and controls under specific genotype models. Especially for rs6935076 ($P_{\text{adjusted}}=0.020$ under dominant model; $P_{\text{adjusted}}=0.028$ under additive model) and rs3756821 ($P_{\text{adjusted}}=0.021$ under additive model), which still associated with dyslexia after Bonferroni correction. The linkage disequilibrium analysis showed four block within gene KIAA0319 and only the ten-maker haplotype ($P=0.013$) in block 4 was significantly more common in dyslexia children than in controls. The results indicated that genetic polymorphisms of KIAA0319 are associated with increased risk of developmental dyslexia in Uyghur population.

¹Corresponding author: Department of Medical School, University of Shihezi, Xinjiang, China,832002.

E-mail: zuo_pengxiang@sina.com

KEYWORDS Developmental dyslexia; KIAA0319; Polymorphisms; Uyghur; Association studies

INTRODUCTION

Developmental dyslexia (DD) is a complex neuro-genetic disorder associated with impairment of reading performance despite adequate educational and intelligence opportunities, as well as in the absence of sensory or neurological disability. It is a common reading disability with the prevalence estimated to be 5%-17% of school-aged children in Western countries(Cope et al. 2005; Pennington and Bishop 2009). The corresponding figure for China, where the previous studies were carried out are reported to be 3.9%-8%(Sun et al. 2013). Although the etiology of dyslexia is not very clear, a number of studies shown that genetic factors play an important role in the development of dyslexia(Cope et al. 2005; Meng et al. 2005; Taipale et al. 2003; Hannula-Jouppi et al. 2005). So far, there are more than nine dyslexia susceptibility loci have been mapped and allocated based on linkage studies (From DYX1 to DYX9). Subsequent association studies have identified several candidate genes at most of these locus, including KIAA0319(Cope et al. 2005), DCDC2(Meng et al. 2005), DYX1C1(Taipale et al. 2003) and ROBO1(Hannula-Jouppi et al. 2005).

KIAA0319, located at chromosomes 6p22.2-22.3. It is first proposed by Kaplan et al. (Kaplan et al. 2002), who found a microsatellite marker residing in KIAA0319 according to linkage studies. Then, dyslexia-KIAA0319 association studies are conducted in US(Francks et al. 2004), UK(Harold et al. 2006; Cope et al. 2005), German(Ludwig et al. 2008), Canadian(Couto et al. 2010; Elbert et al. 2011), Indian(Venkatesh et al. 2011; Venkatesh et al. 2013) and Chinese(Lim et al. 2014; Sun et al. 2014) population, suggesting several risk SNPs are associated with reading disability, such as rs4504469, rs6935076 and rs2038137. However, the results are not

always consistent since the difference of genetic and linguistic between ethnic groups. KIAA0319 gene is expressed in human cerebral neocortex(Paracchini et al. 2006). The protein encoded by KIAA0319 has a large, highly N-and O-glycosylated plasma membrane and is involved in abnormal regulation of neuronal migration and neurite growth through endocytosis pathway of the protein and proteolytic processing(Velayos-Baeza et al. 2008; Levecque et al. 2009; Velayos-Baeza et al. 2010), which is considered to be an important feature of dyslexia(Gabel et al. 2010; Poelmans et al. 2011). However, both the exact pathogenesis of candidate gene KIAA0319 and the mechanism of dyslexia associated KIAA0319 polymorphisms are remains complicated.

Thus far, most studies on dyslexia associated polymorphisms have been performed in European and Chinese populations and few covers individuals of Uyghurian descent. The Uyghur, accounts for 48% of the whole group in Xinjiang with 11 million population, is the second largest minority ethnic group in China, mainly live in Xinjiang Uyghur Autonomous region, areas are located in far northwest of China(Statistic Bureau of Xinjiang Uyghur Autonomous 2014). It is a population presenting a typical mixed genetic origin, both Eastern and Western anthropometric traits (Black et al. 2006; Wang et al. 2003). Uighurs have their own inheritance, culture, religion and language, which are very different from other ethnic populations. Based on our previous epidemiology and genetic studies, we performed case-control association study among a large unrelated Chinese Uyghur cohort in the present research, to investigate whether there is also an association of KIAA0319 gene polymorphisms and Uyghur dyslexia children.

MATERIALS AND METHODS

Experimental subjects

We selected 4251 Uyghur primary students aged 8-13 years by cluster sampling in Kashgar and Aksu, Xinjiang, China. The study was approved by the ethical committee of The Medical School of Shihezi University. Informed written consents were obtained from all participants students and their guardians. The diagnostic criteria for dyslexia were based on the following criteria: ①the score of *The Pupil Rating Scale Revised Screening for Learning Disability* was lower than 65 points(Jing et al. 1998); ②a score on *The Dyslexia Checklist for Uyghur Children* at least two standard deviations higher than the mean score(Wu et al. 2006); ③an intelligence quotient score was higher than 80 assessed by *China-Wechsler Intelligence Scale for Children*(Gong and Dai 1987); and ④in the absence of visual and/or auditory disorders or psychiatric diseases. In total, 228 Uyghur students were diagnosed as dyslexic and 196 of which were participant in the present study, with a total 122 boys and 74 girls, aged between 8 and 12 years(mean age=10.99±1.1 years). Then age-, education-, gender- and ethnicity-matched 196 normal children were also recruited for the case-control study.

Genotyping

A total of eighteen SNPs of KIAA0319 were selected in the present study for the following reasons. ①The minor allele frequencies (MAF) of these eighteen SNPs were more than 0.05 in both HapMap CHB data and HapMap CEU data. ②These polymorphisms were reported to be associated with dyslexia in previous study among Indo-European(rs4504469; rs2038137; rs6935076; rs2179515; rs3212236; rs761100; rs9461045)(Cope et al. 2005; Harold et al. 2006; Couto et al. 2010; Venkatesh et al.

2013) and Chinese language(rs1091031; rs699463; rs3903801; rs12193738; rs2760157; rs807507; rs16889506; rs9366577; rs16889556; rs2038139; rs3756821)(Sun et al. 2014; Lim et al. 2014).

DNA was extracted from oral mucosal cells by the buccal swabs method as described elsewhere(Zuo et al. 2012). The SNP genotyping work was performed using a custom-by-design 48-Plex SNPscan™ Kit(Cat#: G0104K, Genesky Inc. Shanghai, China) as what mentioned before(Chen et al. 2012). This kit was developed according to patented SNP genotyping technology which is based on double ligation and multiplex fluorescence PCR. Our study data were collected through procedures carried out according to the manufacturer's manual. Each 96-well plate included one non-template control. For quality control, repeated analyses were done for 4% of randomly selected samples with high DNA quality. Call rates for each SNP were above 98%.

Statistical analysis

The Hardy–Weinberg equilibrium(HWE) tests were performed for each SNP. Differences in the distribution of demographic characteristics, selected variables, and genotypes of the 18 SNPs between the cases and controls were evaluated using the χ^2 test. The associations analysis between SNPs genotypes and risk of dyslexia were estimated by computing the ORs and their 95% CIs using logistic regression analyses with dominant, recessive, over-dominant, additive, and genotype models. Besides, Linkage disequilibrium(LD) analysis of eighteen SNPs and haplotype selection were performed using Haploview software (Version 4.2)(Barrett et al. 2005). Bonferroni correction was applied for multiple comparisons. All statistical analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA) and P values were two-tailed with a significance level of 0.05.

RESULTS

Characteristics of the Uyghur population

On the whole, 195 cases and 196 controls were successfully genotyped in the study with a response rate is 99.5% and 100%, respectively. Characteristics of these Uyghur students were summarized in Table 1. The dyslexia and normal students appeared to be adequately matched on age, sex, education and ethnic as suggested by the χ^2 tests ($P > 0.05$). Besides, the primary information of the eighteen genotyped SNPs is shown in Table 2. The MAF of most SNPs in control students was between the MAF of CHB data and CEU data. All the markers showed HWE P -value > 0.05 , except rs16889506 ($P = 0.022$).

Table 1 Distribution of selected demographic variables and risk factors of participants

Variable	Cases(n=195)		Control(n=196)		χ^2	P
	n	%	n	%		
Age					0.124	0.725
≤ 10 years	76	38.97	73	37.24		
≥ 11 years	119	61.03	123	62.76		
Sex					0.346	0.556
Boys	125	64.10	120	61.22		
Girls	70	35.90	76	38.78		
Grade					0.005	0.998
Three	56	28.72	56	28.57		
Four	69	35.38	70	35.71		
Five	70	35.90	70	35.71		

Table 2 List of SNPs and HWE's of *KIAA0319* analyzed by SNPscan in the present study

SNP	Regulome DB	Allele	Position	Location	CHB/CEU ^b	Control	HWE ^d
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	score ^a				MAF ^c	MAF	
rs1091031	No Data	G/A	24539139	3 'downstream	0.193/0.438	0.298	1.000
rs699463	4	G/A	24544903	Exon21	0.121/0.239	0.184	1.000
rs3903801	5	A/G	24559433	Intron16	0.246/0.429	0.327	0.330
rs12193738	No Data	T/C	24568393	Intron13	0.215/0.473	0.324	0.145
rs2760157	5	G/A	24578272	Exon 9	0.489/0.183	0.332	0.262
rs807507	No Data	C/G	24579867	Intron 8	0.178/0.483	0.309	0.093
rs4504469	No Data	C/T	24588884	Exon 4	0.019/0.306	0.250	0.339
rs16889506	1f	T/C	24595853	Intron 3	0.109/0.186	0.219	0.022
rs2179515	No Data	C/T	24628203	Intron 1	0.113/0.385	0.265	0.714
rs761100	6	C/A	24632642	Intron 1	0.130/0.455	0.304	0.502
rs9366577	No Data	T/C	24641328	Intron 1	0.073/0.150	0.082	0.120
rs16889556	No Data	C/T	24641605	Intron 1	0.201/0.155	0.122	1.000
rs6935076	5	C/T	24644322	Intron 1	0.230/0.262	0.212	0.668
rs2038139	No Data	A/C	24645420	Intron 1	0.122/0.332	0.265	1.000
rs2038137	2b	G/T	24645943	5' UTR	0.234/0.334	0.265	1.000
rs3756821	4	C/T	24646821	5' UTR	0.411/0.362	0.276	0.593
rs3212236	5	T/C	24648455	Promoter	0.358/0.358	0.452	0.774
rs9461045	No Data	C/T	24649061	Promoter	0.481/0.221	0.452	0.774

a:<http://www.regulomedb.org/>.

b: CHB/CEU: Han Chinese in Beijing, China/ Utah residents with ancestry from northern and western Europe

c:MAF: minor allele frequency.

d:HWE: Hardy–Weinberg equilibrium.

Associations between polymorphisms and risk of dyslexia

In the present study, seven of the eighteen KIAA0319 polymorphisms showed nominal association with dyslexia after genotyping (results shown in Table 3). Allelic frequencies of six SNPs(rs1091031: $P=0.034$; rs16889556: $P=0.010$; rs6935076: $P=0.001$; rs3756821: $P=0.001$; rs3212236: $P=0.009$; rs9461045: $P=0.009$) were significant different between dyslexia and control students. Furthermore, the minor allele(T) frequency of rs6935076 with $P=0.026$ and T allele of rs3756821 with $P=0.023$ also displayed a strong association with dyslexia after applying Bonferroni's correction.

Table 3 also shows genotype distributions under various genotype models of these seven risk SNPs. The results showed significant association of rs1091031 in dominant model($P=0.042$) and additive model($P=0.033$). SNP rs9366577 demonstrated nominal significant association under over-dominant model($P=0.024$). SNP rs16889556 showed significant association under dominant($P=0.007$), over-dominant($P=0.012$), additive model($P=0.009$) and in heterozygous genotype of co-dominant model($P=0.010$). Similarly, SNP rs6935076 manifested nominal meaning association based on dominant($P=0.001$), over-dominant($P=0.009$) and additive model($P=0.001$) as well as in co-dominant model(CT vs CC: $P=0.003$; TT vs CC: $P=0.046$). Besides, significant association was also found for rs3756821 under dominant($P=0.004$), recessive($P=0.021$), additive model($P=0.001$) and co-dominant model(CT vs CC: $P=0.021$; TT vs CC: $P=0.004$). Moreover, SNP rs3212236 and rs9461045 showed equal significant association under dominant($P=0.019$) and additive model($P=0.010$), as well as in homozygous genotype of co-dominant model($P=0.015$). However, after Bonferroni correction for multiple comparisons in different models, only polymorphism rs6935076 under dominant model($P=0.020$) and additive

model($P=0.028$) as well as rs3756821 under additive model($P=0.021$) remain significant difference between dyslexia and controls.

Table 3 Logistic regression analyses of association between KIAA0319 polymorphisms and risk of dyslexia

SNP	Model	Genotype	Case	Control	OR(90%CI)	P	adjust P
rs1091031	Allele	G	245	273	1.381(1.025-1.861)	0.034	0.647
		A	145	117			
	Codominant	G/G	75	95	1 (referent)	-	-
		G/A	95	83	1.450(0.950-2.212)	0.085	1.611
		A/A	25	17	1.863(0.938-3.701)	0.076	1.439
	Dominant	G/G	75	95	1.520(1.016-2.273)	0.042	0.789
		G/A+A/A	120	100			
	Recessive	G/G+G/A	170	178	1.540(0.803-2.953)	0.194	3.681
		A/A	25	17			
	Over-dominant	G/G+A/A	100	112	1.282(0.860-1.911)	0.223	4.233
		G/A	95	83			
	Additive	-	-	-	1.394(1.028-1.891)	0.033	0.618
rs9366577	Allele	T	347	360	1.394(0.862-2.255)	0.176	3.336
		C	43	32			
	Codominant	T/T	152	167	1 (referent)	-	-
		T/C	43	26	-	1.000	19.000
		C/C	0	3	-	1.000	19.000
	Dominant	T/T	152	167	1.629(0.969-2.739)	0.066	1.248
		T/C+C/C	43	29			
	Recessive	T/T+T/C	195	193	-	1.000	19.000

		C/C	0	3			
	Over-dominant	T/T+C/C	152	170	1.850(1.085-3.155)	0.024	0.455
		T/C	43	26			
	Additive	-	-	-	1.403(0.863-2.283)	0.172	3.271
	Allele	C	316	344	1.678(1.132-2.489)	0.010	0.190
		T	74	48			
	Codominant	C/C	126	151	1 (referent)	-	-
		C/T	64	42	1.826(1.158-2.880)	0.010	0.181
		T/T	5	3	1.997(0.468-8.522)	0.350	6.649
rs16889556	Dominant	C/C	126	151	1.838(1.179-2.864)	0.007	0.137
		C/T+T/T	69	45			
	Recessive	C/C+C/T	190	193	1.693(0.399-7.184)	0.475	9.030
		T/T	5	3			
	Over-dominant	C/C+T/T	131	154	1.791(1.138-2.820)	0.012	0.224
		C/T	64	42			
	Additive	-	-	-	1.712(1.142-2.565)	0.009	0.174
	Allele	C	268	309	1.695(1.227-2.342)	0.001	0.026
		T	122	83			
	Codominant	C/C	90	123	1 (referent)	-	-
		C/T	88	63	1.909(1.251-2.913)	0.003	0.051
		T/T	17	10	2.323(1.016-5.313)	0.046	0.869
rs6935076	Dominant	C/C	90	123	1.966(1.313-2.944)	0.001	0.020
		C/T+T/T	105	73			
	Recessive	C/C+C/T	178	186	1.776(0.792-3.984)	0.163	3.101
		T/T	17	10			
	Over-dominant	C/C+T/T	107	133	1.736(1.150-2.620)	0.009	0.164

		C/T	88	63			
	Additive	-	-	-	1.705(1.227-2.371)	0.001	0.028
	Allele	C	240	284	1.644(1.216-2.221)	0.001	0.023
		T	150	108			
	Codominant	C/C	72	101	1 (referent)	-	-
		C/T	96	82	1.642(1.077-2.505)	0.021	0.404
		T/T	27	13	2.913(1.408-6.030)	0.004	0.075
rs3756821	Dominant	C/C	72	101	1.816(1.213-2.720)	0.004	0.072
		C/T+T/T	123	95			
	Recessive	C/C+C/T	168	183	2.262(1.130-4.529)	0.021	0.401
		T/T	27	13			
	Over-dominant	C/C+T/T	99	114	1.348(0.904-2.010)	0.142	2.707
		C/T	96	82			
	Additive	-	-	-	1.681(1.230-2.298)	0.001	0.021
	Allele	T	250	215	0.680(0.511-0.906)	0.009	0.162
		C	140	177			
	Codominant	T/T	82	60	1 (referent)	-	-
		T/C	86	95	0.662(0.425-1.031)	0.068	1.296
		C/C	27	41	0.482(0.267-0.868)	0.015	0.287
rs3212236	Dominant	T/T	82	60	0.608(0.401-0.922)	0.019	0.362
		T/C+C/C	113	136			
	Recessive	T/T+T/C	168	155	0.608(0.357-1.035)	0.067	1.267
		C/C	27	41			
	Over-dominant	T/T+C/C	109	101	0.839(0.563-1.249)	0.387	7.348
		T/C	86	95			
	Additive	-	-	-	0.688(0.518-0.915)	0.010	0.193

rs9461045	Allele	C	250	215	0.680(0.511-0.906)	0.009	0.162
		T	140	177			
	Codominant	C/C	82	60	1 (referent)	-	-
		C/T	86	95	0.662(0.425-1.031)	0.068	1.296
		T/T	27	41	0.482(0.267-0.868)	0.015	0.287
	Dominant	C/C	82	60	0.608(0.401-0.922)	0.019	0.362
		C/T+T/T	113	136			
	Recessive	C/C+C/T	168	155	0.608(0.357-1.035)	0.067	1.267
		T/T	27	41			
	Over-dominant	C/C+T/T	109	101	0.839(0.563-1.249)	0.387	7.348
	C/T	86	95				
Additive	-	-	-	0.688(0.518-0.915)	0.010	0.193	

Haplotype analysis

Four detected LD blocks within gene KIAA0319 are shown in Fig. 1 according to D' value. Table 4 indicates the frequency of the CCTTTAGTTC haplotype of block 4 in dyslexia group was significantly higher than that in control group ($P=0.013$) and implies that this haplotype was a risk haplotype to dyslexia. Except for block 4, we did not find any significant haplotypes in all the other three blocks.

Table 4 Selected haplotype analysis results of KIAA0319

Haplotype	Case	Control	OR (95%CI)	P-value
Block 1: rs699463-rs3903801				
GA	190	192	-	-
GG	114	128	0.9000(0.6520-1.2424)	0.5218
AA	86	72	1.2070(0.8322-1.7506)	0.3213
Block 2: rs12193738-rs2760157-rs807507				

TGC	159	136	-	-
TAC	110	129	0.7294(0.5180-1.0270)	0.2364
CGG	115	121	0.8129(0.5770-1.1454)	0.0707
Block 3: rs4504469-rs16889506				
CT	195	208	-	-
TT	95	98	1.0340(0.7336-1.4574)	0.8485
CC	100	86	1.2403(0.8756-1.7569)	0.2254
Block 4: rs2179515-rs761100-rs9366577-rs16889556-rs6935076-rs2038139-rs2038137-rs3756821-rs3212236-rs9461045				
TATCCCTCTC	89	103	-	-
CCTCCAGCCT	140	176	1.0597(0.6955-1.6145)	0.7872
CCTTTAGTTC	73	47	1.7975(1.1308-2.8573)	0.0131

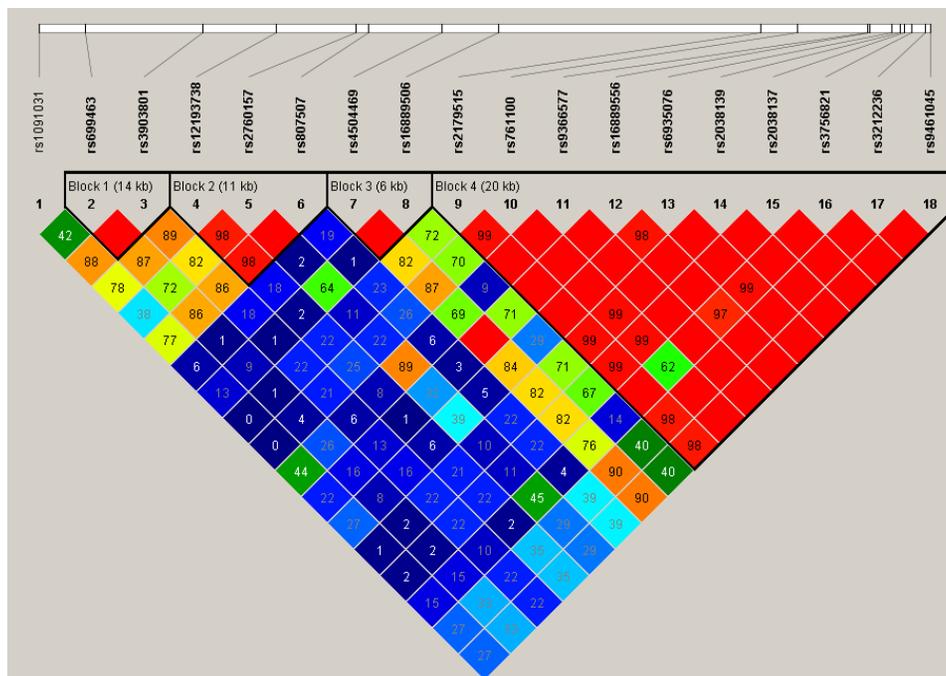


Figure1 Linkage disequilibrium (LD) block generated by the Haploview 4.1. Regions of low-to-high LD, as measured by the D' statistic, were represented by deep blue to

red shading, respectively. LD blocks were analyzed using an algorithm by Gabriel et al.(Gabriel et al. 2002)

DISCUSSION

Up to now, there are numerous studies focused on dyslexia associated KIAA0319 polymorphisms. However, these studies mainly performed in European, Indian and Han Chinese populations and the results are inconclusive. Take the genetic and linguistic differences between Uyghur and other populations into consideration, here we selected eighteen tag SNPs of gene KIAA0319 followed by high-throughput sequencing to assess the association of polymorphisms and dyslexia in a large unrelated Uyghur cohort. In summary, we identified seven KIAA0319 polymorphisms and one haplotype have nominal association with dyslexia after genotyping. Especially for rs3756821 and rs6935076, the results survived Bonferroni correction for multiple comparisons. To our knowledge, this study is first to explore the role of KIAA0319 in dyslexia in a relatively large Uyghur populations.

This study included frequently reported polymorphisms by previous study among Chinese and Indo-European language. The rs3756821, located at 5' UTR of gene KIAA0319, showed nominal association with dyslexia in recent studies in Chinese populations but failed showed significant association after Bonferroni correction(Lim et al. 2014; Sun et al. 2014). While the results from the present study indicate the association between rs3756821 and Uyghur dyslexia after correction. Therefore, it implies that rs3756821 is a risk SNP to dyslexia in Uyghur population not in Chinese. This may be attributed to the fact that the genetic and linguistic among Uyghur and

Chinese might be different, which could cause the susceptibility gene conduce to dyslexia through different mechanisms(Kirsten et al. 2012). Compared to Chinese, Uyghur form an isolated genetic group because of the Uyghur population is less influenced by recent migration(Black et al. 2006) and Uyghur are overwhelmingly Muslim, who prohibits marriage to non-Muslims(Li 2012). For language, Uyghur, an alphabetical language, belongs to the Altaic family with linear one-dimensionally arranged alphabetic(Xi et al. 2015), which is dislike Chinese (ideograph language) in linguistic characteristics(Siok et al. 2008). Besides, previous studies found that the cerebral regions activated by Uyghur and Chinese language are not identical and identified the left anterior cinugulate gyrus might associated with Uyghur language(Xi et al. 2015).

We also find significant association of rs6935076, a previously identified causative polymorphism with dyslexia. rs6935076 is located in intron 1 of the gene KIAA0319 and has the role to explain dyslexia status in the research done by Cope et al. among UK populations(Cope et al. 2005). However, several previous association study(Brkanac et al. 2007) and our early meta analysis failed to replicate the association of rs6935076 and dyslexia. Except for rs3756821 and rs6935076, other selected polymorphisms seem unlikely contributing to dyslexia susceptibility among Uyghur children after Bonferroni correction, whereas the results are inconclusive across different populations(Venkatesh et al. 2013; Elbert et al. 2011; Sun et al. 2014). The genetic and linguistic also could account for this results. We have mentioned that Uyghur presenting a typical mixed genetic origin and is an isolated genetic group.

Uyghur and English both are part of an alphabetical language, but Uyghur has its own written forms and rules for writing and it is more complex than English(Siok et al. 2008). Even our findings reveal that rs3756821 and rs6935076 have significant difference between dyslexia and control group, the mechanism of these variants in Uyghur dyslexics is still unclear.

It is generally believed that combined variants within a gene may provide a more comprehensive evaluation than a single polymorphism in association studies(Pan et al. 2010). Based on the analysis of haplotypic, we think that the susceptibility haplotype (CCTTTAGTTC) constructed by ten SNP has an independent effect on dyslexia(P=0.013). However, we should take care of the results to assess the association between the haplotype and dyslexia because Fallin et al.(Fallin and Schork 2000) suggested that deviation from HWE with a high level of heterozygosity may produce error genetic effect of haplotype. Therefore, we concluded that children who carry more risk alleles are more likely to develop dyslexia than those who carry fewer or none.

While the present study provides valuable insight into the genetic differences of dyslexia in minority group, several limitations need to be addressed. First of all, the SNPs selection were based on previous study, we devoted ourselves to verified whether these polymorphisms have the same effect on Uyghur dyslexia children, which may not give a comprehensive view about genetic variability of KIAA0319 in Uyghur population. Secondly, the moderate sample size could limited the statistic power of this study. There were actually more dyslexia children included in the present study, but only 86% of dyslexia children were participate in the study due to the people of minority group often refuse to join in scrape the oral mucosal. Moreover, dyslexia is a multiple etiology disease, the existence of the interaction between

environmental factors and the dyslexia susceptibility loci, as well as the interaction between different candidate genes must be further validated in the Uyghur population.

In conclusion, we performed association study of KIAA0319 with dyslexia in a large unrelated Uyghur cohort through SNPs selection and genotyping. Our study suggested that seven polymorphisms and one haplotype of KIAA0319 have significant association with the risk of dyslexia. Especially for rs6935076 and rs3756821, which still associated with dyslexia after Bonferroni correction. Results could contribute to early identification and management of Uyghur children with dyslexia, as well as to research into dyslexia and different racial genetics. Moreover, to better explicate the role of KIAA0319 underlying dyslexia etiology and pathology, more functional studies in Uyghur population need to be conducted.

ACKNOWLEDGMENTS

This study was supported in part by National Natural Science Foundation of China(81360434). We wish to thank Dr. Da Ding and Dr. Yan Liu (Genesky Biotechnologies Inc., Shanghai, China) for technical support.

LITERATURE CITED

- Barrett, J.C., B. Fry, J. Maller, and M.J. Daly, 2005 Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 21 (2):263-265.
- Black, M.L., C.A. Wise, W. Wang, and A.H. Bittles, 2006 Combining genetics and population history in the study of ethnic diversity in the People's Republic of China. *Human Biology* 78 (3):277-293.
- Brkanac, Z., N.H. Chapman, M.M. Matsushita, L. Chun, K. Nielsen *et al.*, 2007 Evaluation of candidate genes for DYX1 and DYX2 in families with dyslexia.

- American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*
144B:556-560.
- Chen, X., S. Li, Y. Yang, X. Yang, Y. Liu *et al.*, 2012 Genome-wide association study validation identifies novel loci for atherosclerotic cardiovascular disease. *Journal of Thrombosis and Haemostasis* 10 (8):1508-1514.
- Cope, N., D. Harold, G. Hill, V. Moskvina, J. Stevenson *et al.*, 2005 Strong Evidence That KIAA0319 on Chromosome 6p Is a Susceptibility Gene for Developmental Dyslexia. 109:581-591.
- Couto, J.M., I. Livne-Bar, K. Huang, Z. Xu, T. Cate-Carter *et al.*, 2010 Association of reading disabilities with regions marked by acetylated H3 histones in KIAA0319. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* 153B:447-462.
- Elbert, A., M.W. Lovett, T. Cate-Carter, A. Pitch, E.N. Kerr *et al.*, 2011 Genetic variation in the KIAA0319 5' region as a possible contributor to dyslexia. *Behavior Genetics* 41:77-89.
- Fallin, D., and N.J. Schork, 2000 Accuracy of Haplotype Frequency Estimation for Biallelic Loci, via the Expectation-Maximization Algorithm for Unphased Diploid Genotype Data. *American journal of human genetics* 67 (4):947-959.
- Francks, C., S. Paracchini, S.D. Smith, A.J. Richardson, T.S. Scerri *et al.*, 2004 A 77-Kilobase Region of Chromosome 6p22 . 2 Is Associated with Dyslexia in Families From the United Kingdom and From the United States.1046-1058.
- Gabel, L.A., C.J. Gibson, J.R. Gruen, and J.J. LoTurco, 2010 Progress towards a cellular neurobiology of reading disability. *Neurobiology of Disease* 38:173-180.
- Gabriel, S.B., S.F. Schaffner, H. Nguyen, J.M. Moore, J. Roy *et al.*, 2002 The structure of haplotype blocks in the human genome. *Science* 296 (5576):2225-2229.

- Gong, Y.X., and X.Y. Dai, 1987 The test analysis of China-Wechesler Young Children Scale of Intelligence. in *The sixth national psychology conference abstract collection*, edited by L. Stubbs.
- Hannula-Jouppi, K., N. Kaminen-Ahola, M. Taipale, R. Eklund, J. Nopola-Hemmi *et al.*, 2005 The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. *PLoS genetics* 1 (4):467-474.
- Harold, D., S. Paracchini, T. Scerri, M. Dennis, N. Cope *et al.*, 2006 Further evidence that the KIAA0319 gene confers susceptibility to developmental dyslexia. *Molecular psychiatry* 11:1085-1091, 1061.
- Jing, J., Y. Sen, and Y. Hai, 1998 The revision and evaluation of pupil rating scale revised screening for learning disability. *Chinese Journal of Child Care* 9:197-200.
- Kaplan, D.E., J. Gayan, J. Ahn, T.W. Won, D. Pauls *et al.*, 2002 Evidence for linkage and association with reading disability, on 6p21.3-22. *American journal of human genetics* 70 (5):1287-1298.
- Kirsten, H., A. Wilcke, C. Ligges, J. Boltze, and P. Ahnert, 2012 Association study of a functional genetic variant in KIAA0319 in German dyslexics. *Psychiatric Genetics* 22 (4):216-217.
- Levecque, C., A. Velayos-Baeza, Z.G. Holloway, and A.P. Monaco, 2009 The dyslexia-associated protein KIAA0319 interacts with adaptor protein 2 and follows the classical clathrin-mediated endocytosis pathway. *American Journal of Physiology-Cell Physiology* 297 (1):C160-C168.
- Li, X., 2012 Survey of intermarriage in rural area of southern Xinjiang province. *Xinjiang academy of social sciences*:59-66.

- Lim, C.K.-P., A.M.-B. Wong, C.S.-H. Ho, and M.M.-Y. Waye, 2014 A common haplotype of KIAA0319 contributes to the phonological awareness skill in Chinese children. *Behavioral and brain functions : BBF* 10:23-23.
- Ludwig, K.U., D. Roeske, J. Schumacher, G. Schulte-Körne, I.R. Köhne *et al.*, 2008 Investigation of interaction between DCDC2 and KIAA0319 in a large German dyslexia sample. *Journal of Neural Transmission* 115 (11):1587-1589.
- Meng, H., S.D. Smith, K. Hager, M. Held, J. Liu *et al.*, 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.
- Pan, Y., J. Ma, W. Zhang, Y. Du, Y. Niu *et al.*, 2010 IRF6 Polymorphisms Are Associated With Nonsyndromic Orofacial Clefts in a Chinese Han Population. *American Journal of Medical Genetics Part A* 152a (10):2505-2511.
- Paracchini, S., A. Thomas, S. Castro, C. Lai, M. Paramasivam *et al.*, 2006 The chromosome 6p22 haplotype associated with dyslexia reduces the expression of KIAA0319 , a novel gene involved in neuronal migration. *Human molecular genetics* 15:1659-1666.
- Pennington, B.F., and D.V.M. Bishop, 2009 Relations among speech, language, and reading disorders. *Annual Review of Psychology* 60:283-306.
- Poelmans, G., J. Buitelaar, D. Pauls, and B. Franke, 2011 A theoretical molecular network for dyslexia: integrating available genetic findings. *Molecular psychiatry* 16 (4):365-382.
- Siok, W.T., Z. Niu, Z. Jin, C.A. Perfetti, and L.H. Tan, 2008 A structural-functional basis for dyslexia in the cortex of Chinese readers. *Proceedings of the National Academy of Sciences of the United States of America* 105 (14):5561-5566.

- Statistic Bureau of Xinjiang Uyghur Autonomous, R., 2014 Available at: <http://www.xjtj.gov.cn/sjcx>. Accessed April 5,2015.
- Sun, Y., Y. Gao, Y. Zhou, H. Chen, G. Wang *et al.*, 2014 Association Study of Developmental Dyslexia Candidate Genes DCDC2 and KIAA0319 in Chinese Population.
- Sun, Z., L. Zou, J. Zhang, S. Mo, S. Shao *et al.*, 2013 Prevalence and Associated Risk Factors of Dyslexic Children in a Middle-Sized City of China: A Cross-Sectional Study. *Plos One* 8 (2).
- Taipale, M., N. Kaminen, J. Nopola-Hemmi, T. Haltia, B. Myllyluoma *et al.*, 2003 A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proceedings of the National Academy of Sciences of the United States of America* 100 (20):11553-11558.
- Velayos-Baeza, A., C. Levecque, K. Kobayashi, Z.G. Holloway, and A.P. Monaco, 2010 The Dyslexia-associated KIAA0319 Protein Undergoes Proteolytic Processing with gamma-Secretase-independent Intramembrane Cleavage. *Journal of Biological Chemistry* 285 (51):40148-40162.
- Velayos-Baeza, A., C. Toma, S. Paracchini, and A.P. Monaco, 2008 The dyslexia-associated gene KIAA0319 encodes highly N- and O-glycosylated plasma membrane and secreted isoforms. *Human molecular genetics* 17:859-871.
- Venkatesh, S.K., A. Siddaiah, and M.Á.D.Á.K.Á. Dcdc, 2011 An Examination of Candidate Gene SNPs for Dyslexia in an Indian Sample.105-109.
- Venkatesh, S.K., A. Siddaiah, P. Padakannaya, and N.B. Ramachandra, 2013 Analysis of genetic variants of dyslexia candidate genes KIAA0319 and DCDC2 in Indian population. *Journal of human genetics* 58:531-538.

- Wang, W., C. Wise, T. Baric, M.L. Black, and A.H. Bittles, 2003 The origins and genetic structure of three co-resident Chinese Muslim populations: the Salar, Bo'an and Dongxiang. *Human genetics* 113 (3):244-252.
- Wu, H.R., R.R. Song, and B. Yao, 2006 Preliminary establishment of Dyslexia Checklist for Chinese Children scale. *Journal of human genetics* 27:189-190.
- Xi, Y.-l., Q. Tian, T. Tuerxun, K. Kaheman, C.-h. Jiang *et al.*, 2015 Comparison of functional magnetic resonance imaging in cerebral activation between normal Uygur and Mandarin participants in semantic identification task. 8:13724-13731.
- Zuo, P.-x., H.-r. Wu, Z.-c. Li, X.-d. Cao, L.-j. Pang *et al.*, 2012 Association of polymorphisms in the DCDC2 gene with developmental dyslexia in the Han Chinese. *Chinese Medical Journal* 125 (4):622-625.

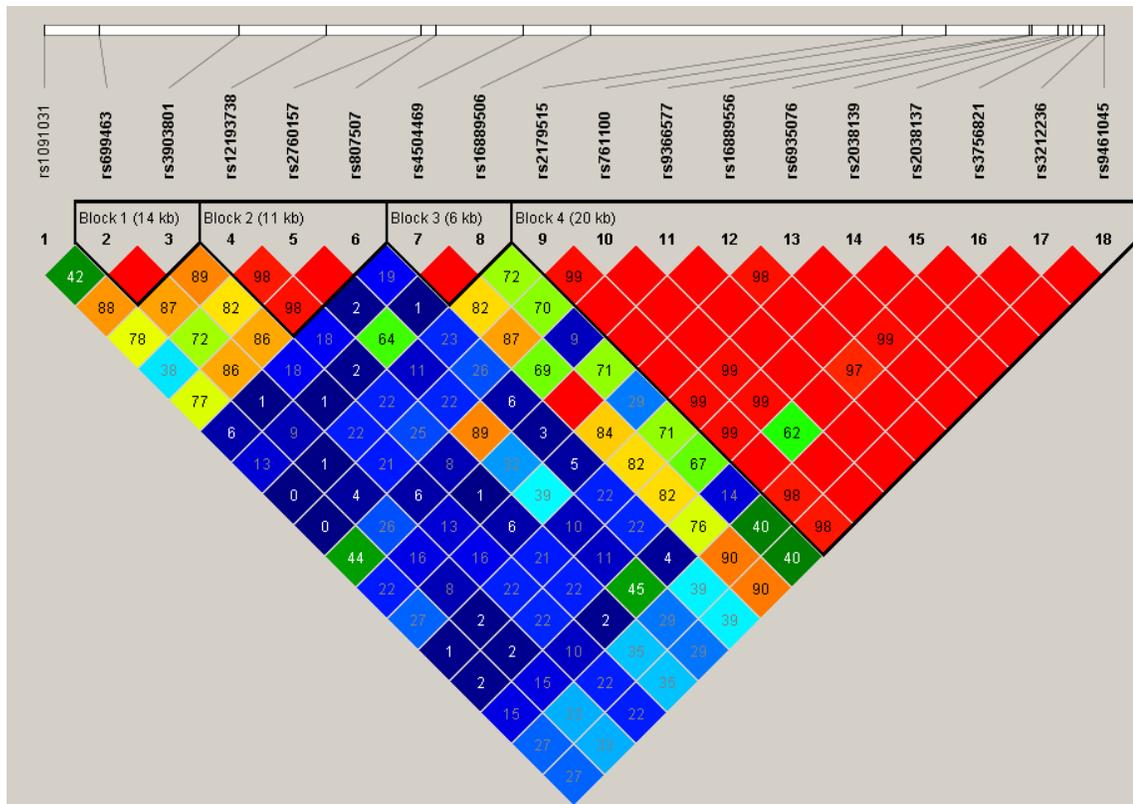


Figure1 Linkage disequilibrium (LD) block generated by the Haploview 4.1. Regions of low-to-high LD, as measured by the D' statistic, were represented by deep blue to red shading, respectively. LD blocks were analyzed using an algorithm by Gabriel et al. (Gabriel et al. 2002)