Association of specific language impairment candidate genes CMIP and ATP2C2 with developmental dyslexia in Chinese population

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ABSTRACT

Developmental dyslexia (DD) and specific language impairment (SLI) are distinct language disorders. Their phenotypic overlap and co-morbidity are frequently reported. In addition, numerous evidences indicate that genetic factors play an important role in DD and SLI. Therefore, it is worthwhile to identify possible genetic linkage shared by these two disorders. Here, we selected 178 Tag SNPs from two SLI candidate genes (CMIP and ATP2C2) and performed high density genotyping in a large unrelated Chinese DD cohort with 502 dyslexic cases and 522 healthy controls. Although some SNPs showed significant association (Pmin = 0.0016) with DD

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through case–control based association analysis, none of them survived Bonferroni correction for multiple comparisons. Thus, the association of SLI candidate genes CMIP and ATP2C2 with DD in Chinese population should be further validated and their contribution to DD should be interpreted with caution.

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1. Introduction

Developmental dyslexia (DD) is a language related learning disability characterized by unexpected difficulties in reading and spelling despite of adequate intelligence, educational backgrounds and intact neurological functions (Paracchini, Scerri, & Monaco, 2007). As a common developmental disorder in children and adolescents, the prevalence of DD ranges from 5% to 17.5% (Shaywitz, 1998). Specific language impairment (SLI) is a developmental disorder characterized by delayed or permanently impaired language acquisition in which no obvious cause could be found (Newbury, Fisher, & Monaco, 2010). The overall prevalence of SLI was reported to be 7.4% among English-speaking kindergarten children (Tomblin et al., 1997). DD and SLI have been categorized into distinct disorders but their phenotypic overlap and co-morbidity are frequently reported. Reading ability and non word repetition (NWR) are recognized as the most informative trait for DD and SLI respectively. Children with poor reading ability may have problems on NWR, and vice versa. Although underlying molecular mechanism of these two disorders are yet to be understood, it was believed that language disorders are distinct but related, in particular for DD and SLI (Pennington & Bishop, 2009).

In recent years, there are increasing evidences leading to a consensus that both DD and SLI are genetic disorders (Newbury et al., 2010; Poelmans, Buitelaar, Pauls, & Franke, 2011). To date, nine dyslexia susceptibility loci, namely DYX1 to DYX9, have been identified (Scerri & Schulte-Koene, 2010). Subsequent refinement of these loci proposed several genes which might contribute to DD. As such, DYX1C1 (Taipale et al., 2003) at DYX1, DCDC2 (Meng et al., 2005) and KIAA0319 (Cope et al., 2005; Francks et al., 2004) at DYX2, and ROBO1 (Hannula-Jouppi et al., 2005) at DYX5 showed strong evidence therefore were recognized as DD candidate genes. In the mean time, SLI1 to SLI5 have been identified as SLI susceptibility loci in which CMIP and ATP2C2 at SLI1 (Newbury et al., 2009), CNTNAP2 at SLI4 (Vernes et al., 2008) were recognized as SLI candidate genes. Thus, there have been compelling evidences implicating the role of genetic factors in DD and SLI. Given their phenotypic overlap and co-morbidity, it is worthwhile to identify possible genetic etiology shared by both disorders.

In the present study, we focused on SLI1, the most studied SLI locus, and performed association study in DD cohort. SLI1, located on chromosome 16q, was identified through family based genome-wide scan with language-related measures (Newbury et al., 2002). The contribution of SLI1 to SLI susceptibility was also supported by follow-up studies (Monaco, 2007; Newbury et al., 2004). In particular, SLI1 showed significant evidence for its linkage with NWR, an important measurement of SLI (Newbury et al., 2002, 2004). The high density screen of SLI1 identified CMIP and ATP2C2 which showed significant association with NWR in either family-based or independent case–control based cohort (Newbury et al., 2009). Therefore, CMIP and ATP2C2 were identified as SLI candidate genes as they contribute to SLI independently by modulating phonological short-term memory (Newbury et al., 2009).

The association of CMIP with reading ability was reported in SLI families (Newbury et al., 2011) and in general population unselected for either SLI or DD (Scerri et al., 2011). However, ATP2C2 failed to associate with reading related traits in either SLI families (Newbury et al., 2011) or general population (Scerri et al., 2011). As for DD research, reading ability has been recognized as the most informative trait for DD. To our knowledge, the only association study between SLI candidate genes and DD did not identify any association of CMIP and ATP2C2 in DD families (Newbury et al., 2011). Therefore, it is worthwhile to replicate their genetic association with DD in a large cohort. Herein, we performed case–control based association analysis of CMIP and ATP2C2 with DD in a large, unrelated Chinese cohort. Our preliminary results showed weak association between the two SLI candidate genes and DD,
Table 1
Demographic information of participants.

| Grade | Dyslexic cases | Controls | Total |
|-------|----------------|----------|-------|
|       | Subjects | Male/ | Age | Nonverbal | Subjects | Male/ | Age | Nonverbal | Subjects | Male/ | Age | Nonverbal |
|       |         | female | (months) | intelligence |         | female | (months) | intelligence |         | female | (months) | intelligence |
| 2     | 72      | 51/21  | 94.17 | 31.58     | 108     | 58/50  | 95.14 | 42.85     | 180     | 109/71 | 94.75 | 38.32     |
| 3     | 81      | 62/19  | 106.79 | 36.43     | 107     | 38/69  | 106.22 | 45.86     | 188     | 100/88 | 106.45 | 41.80     |
| 4     | 92      | 68/24  | 121.05 | 40.25     | 129     | 50/79  | 119.38 | 47.38     | 221     | 118/103 | 120.01 | 44.41     |
| 5     | 129     | 101/28 | 130.60 | 43.16     | 84      | 34/50  | 130.13 | 48.60     | 213     | 135/78 | 130.41 | 45.31     |
| 6     | 128     | 109/19 | 143.17 | 45.51     | 94      | 41/53  | 140.72 | 50.62     | 222     | 150/72 | 142.16 | 47.67     |
| Total | 502     | 391/111| 122.99 | 40.48     | 522     | 221/301| 117.28 | 46.92     | 1024    | 612/412 | 118.76 | 43.76     |
Table 2
Selected genotyping results of CMIP and ATP2C2.

| Gene | SNP     | Model | Patient | Control | OR (95%CI) | P       | OR adjusted (95%CI) | P adjusted |
|------|---------|-------|---------|---------|------------|--------|---------------------|----------|
| CMIP | rs1563654 | n = 480 | 86.46%  | 83.10%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 509 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| CMIP | rs876672 | n = 481 | 72.45%  | 76.82%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 509 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| CMIP | rs8047876 | n = 480 | 75.38%  | 79.12%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 508 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| CMIP | rs765413 | n = 482 | 86.00%  | 80.08%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 507 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| CMIP | rs11640297 | n = 481 | 14.00%  | 19.92%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 508 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| ATP2C2 | rs7350833 | n = 483 | 86.85%  | 90.94%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 508 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| ATP2C2 | rs8046864 | n = 482 | 86.31%  | 90.10%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 510 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
|      |         |         |         |         |            |        |                     |          |
| ATP2C2 | rs12448765 | n = 483 | 82.51%  | 86.64%  | 1.354     | 0.0160 | 0.0014              | 0.0200   |
|      |         | n = 509 |         |         | 1.345     | 0.0160 | 0.0014              | 0.0200   |
but failed to survive Bonferroni correction for multiple comparisons. The common genetic factors shared by DD and SLI remains elusive, therefore should be further investigated.

2. Materials and methods

2.1. Subjects

We recruited 6900 grade two to grade six primary students aged 7 to 13 from Shandong Province. This study was approved by the ethical committee of Tsinghua University School of Medicine. All participants were informed by written consent. The selection of dyslexic cases and controls from these 6900 children was performed in two stages. First, all participants received a Chinese reading test comprising character-, word-, and sentence-level questions. The first stage screening identified 1794 children with reading scores below the 13th percentile and above 87th percentile of their grade eligible for the second stage screening. In the second stage, the 1794 eligible children were further tested individually by a character reading test widely used for Chinese DD research (Siok, Niu, Jin, Perfetti, & Tan, 2008; Siok, Perfetti, Jin, & Tan, 2004; Tan, Xu, Chang, & Siok, 2013). The character reading test was composed of 300 Chinese characters, among which 250 were selected from their textbooks and the other 50 low-frequency items were from a language corpus. The numbers of characters from first to sixth grade textbooks were 20, 30, 40, 50, 60 and 50, respectively. Characters were arranged in a list from easy to difficult based on grade level and visual complexity or stroke number. Children were asked to read the characters aloud as quickly and accurately as possible. Children with reading performance two grades behind the expected reading level were defined as dyslexic cases. Specifically, the expected reading level was calculated by adding together the number of items for the preceding grades and 75% of the items for the actual grade. For example, to meet the criteria for the third grade level, children would need to respond correctly on 80 items (20 for grade one, 30 for grade two and 75% of the 40 items for grade three). For second graders who could not be identified using these criteria, we selected those whose performances were 1.5 SD below grade average. In addition, Raven’s Progressive Matrices test for nonverbal intelligence was applied to these 1794 children individually. Children with nonverbal intelligence scores lower than the 25th percentile were excluded from this study. Finally, there were 1024 children comprising 502 dyslexic cases and 522 healthy controls eligible for subsequent genotyping and association analysis (Table 1).

### Table 2 (continued)

| Gene        | SNP          | Model    | Patient N (%) | Control N (%) | OR (95%CI) | P       | OR adjusted (95%CI) | P adjusted |
|-------------|--------------|----------|---------------|--------------|------------|---------|---------------------|------------|
| AG          | 149 112      |          | 1.5808 (1.1874–2.1047) | 0.0017      | 1.5778 (1.1583–2.1493) | 0.0038  |
| AA          | 10 12        |          | 0.9902 (0.4223–2.3217) | 0.9820      | 0.9247 (0.3705–2.3080) | 0.8668  |
| Dom         |              |          | 1.5240 (1.1550–2.0110) | 0.0029      | 1.5140 (1.1220–2.0430) | 0.0067  |
| Rec         |              |          | 0.8756 (0.3748–2.0460) | 0.7590      | 0.8291 (0.3348–2.0530) | 0.6854  |
| ATP2C2      | rs9929758    |          | n = 470 n = 492 |          | 1         | 1       | 1                   |            |
| T Allele    | 82.55%       |          | 1.2750 (0.9963–1.6310) | 0.0535      | 1.3590 (1.0390–1.7770) | 0.0253  |
| C Allele    | 14.23%       |          | 1                   |            |           |         | 1                   |            |
| TT          | 315 367      |          | 1                  |            |           |         | 1                   |            |
| CT          | 146 110      |          | 1.5464 (1.1575–2.0659) | 0.0322      | 1.6582 (1.2106–2.2711) | 0.0016  |
| CC          | 9 15         |          | 0.6990 (0.3018–1.6193) | 0.4035      | 0.7535 (0.2997–1.8941) | 0.5473  |
| Dom         |              |          | 1.4450 (1.0920–1.9110) | 0.0099      | 1.5550 (1.1470–2.1090) | 0.0045  |
| Rec         |              |          | 0.6208 (0.2690–1.4330) | 0.2639      | 0.6543 (0.2638–1.6230) | 0.3600  |
| ATP2C2      | rs11640169   |          | n = 483 n = 510    |          | 1         | 1       | 1                   |            |
| C Allele    | 92.03%       |          | 1.7098 (0.5066–0.9944) | 0.0463      | 1.7377 (0.5186–1.0490) | 0.0907  |
| T Allele    | 10.39%       |          | 1                   |            |           |         | 1                   |            |
| CC          | 406 411      |          | 1                   |            |           |         | 1                   |            |
| TC          | 77 92        |          | 0.8473 (0.6077–1.1813) | 0.3283      | 0.7807 (0.5463–1.1156) | 0.1740  |
| TT          | 0 7          |          | n.a                 |            | n.a       | n.a     | n.a                 |            |
| Dom         |              |          | 0.7874 (0.5673–1.0930) | 0.1530      | 0.7377 (0.5186–1.0490) | 0.0907  |
| Rec         |              |          | n.a                 |            | n.a       | n.a     | n.a                 |            |

All SNPs were analyzed under allele, genotype, dominant (Dom) and recessive (Rec) models. Statistical analysis was performed using Chi-square test. P < 0.05 were indicated in bold. After Bonferroni correction, none of the associations highlighted in bold remained significant.
2.2. SNP markers selection and genotyping

We selected Tag SNPs of CMIP and ATP2C2 through Tagger program (De Bakker et al., 2005). We applied minor allele frequency (MAF) over 5% and pairwise $r^2$ threshold of 0.8 for Tag SNP selection. In total, 105 Tag SNPs of CMIP and 73 Tag SNPs of ATP2C2 were selected for subsequent genotyping which was performed at CapitalBio Corporation (Beijing, China) with Sequenom MassARRAY platform (San Diego, U.S) according to the manufacturer’s protocol. Briefly, genomic DNA was extracted from saliva of each individual through Oragene™ DNA self-collection kit according to the manufacturer’s instructions (Ottawa, Canada). DNA concentration was determined by NanoDrop 1000 (Waltham, U.S). Specific assays were designed using the MassARRAY Assay Design software package (v3.1). Mass determination was carried out with the MALDI-TOF mass spectrometer and Mass ARRAY Type 4.0 software was used for data acquisition.

2.3. Data analysis

Each SNP was examined by Hardy–Weinberg equilibrium tests (HWE). The association analysis was performed with PLINK software using additive, dominant, recessive and genotype models. Linkage disequilibrium analysis and haplotype selection were performed using Haploview software (Version 4.2) (Barrett, Fry, Maller, & Daly, 2005). The Omnibus ANOVA test was conducted with R software. Logistic regression was used for age and sex stratification. Different methods including Bonferroni, Holm, Hochberg and Hommel as well as False Discovery Rate (FDR) based methods including BH and BHY were applied for multiple comparisons. The results presented here were corrected through Bonferroni correction.

3. Results

3.1. Single marker analysis

In the present study, we performed high density genotyping on 105 Tag SNPs of CMIP and 73 Tag SNPs of ATP2C2. Table 2 showed top five SNPs with additive effects that exceeded significant threshold ($P < 0.05$) after data adjustment for age and sex through logistic regression. The complete genotyping results of CMIP and ATP2C2 are listed in Supplement Tables S1 and S2 respectively.

In CMIP gene, we identified T allele of rs765413 ($P = 0.0028$, OR $= 0.6742$) with minimum $P$ value in case–control analysis. Meanwhile, rs876672, rs11640297, rs8047876 and rs1563654 also showed significant association with DD under additive model (Table 2). In ATP2C2 gene, we identified C allele of rs7350833 ($P = 0.0191$, OR $= 1.4350$) with minimum $P$ value in case–control analysis. Additionally, rs8046864, rs12448765, rs9929758 and rs11640169 showed significant association with DD under additive model as well (Table 2). However, none of these SNPs remain significant after Bonferroni correction for multiple comparisons.

In addition, we also observed a number of SNPs exceeded significant threshold under other models including dominant model, recessive model and genotype model before Bonferroni correction for multiple comparisons (Supplement Tables S1 and S2). However, we did not observe any significant association of previous reported SNPs (Newbury et al., 2009, 2011; Scerri et al., 2011) such as rs12927866, rs16955705, rs6564903 of CMIP and rs16973771, rs2875891 of ATP2C2 with DD in our cohort (data not shown).

3.2. Haplotype analysis

We built 26 blocks within CMIP and 17 blocks within ATP2C2 through Haploview software (Supplement Figures S1 and S2). In CMIP, rs12929303-rs2287112-rs12925980 (OMNIBUS $P = 0.0338$) and rs7186510-rs765413-rs3751859 (OMNIBUS $P = 0.0284$) showed overall significant association with DD in our cohort therefore they might be risk haplotypes contributing to disease susceptibility (Table 3). In addition, we also observed a number of haplotypes in CMIP which exceeded significant threshold in specific genotypes ($P_{\text{min}} = 0.0150$). The complete results of CMIP blocks are listed in...
Table 3
Selected haplotype analysis results of CMIP and ATP2C2.

| Haplotype                        | Logistic regression | OR unadjusted | P unadjusted | OR adjusted | P adjusted |
|----------------------------------|---------------------|---------------|--------------|-------------|------------|
| CMIP: rs12929303-rs2287112-rs12925980
OMNIBUS                         | 0.0282               | NA            | 0.0338       |
| GGT                             | 1.1700               | 0.2120        | 1.1100       | 0.4370      |
| GTT                             | 0.7880               | 0.0158        | 0.7650       | 0.0120      |
| ATC                             | 0.9050               | 0.3630        | 0.9340       | 0.5650      |
| GTC                             | 1.2300               | 0.0244        | 1.2800       | 0.0164      |
| CMIP: rs7186510-rs765413-rs3751859
OMNIBUS                         | 0.0096               | NA            | 0.0284       |
| GCA                             | 1.0500               | 0.5950        | 1.0200       | 0.8300      |
| ATG                             | 0.6680               | 0.0010        | 0.6900       | 0.0053      |
| ACG                             | 1.0600               | 0.6200        | 1.0400       | 0.7560      |
| GCG                             | 1.2000               | 0.0579        | 1.2300       | 0.0454      |
| ATP2C2: rs2326254-rs4782946-rs8046864
OMNIBUS                         | 0.0571               | NA            | 0.2430       |
| TTC                             | 1.5100               | 0.0043        | 1.4000       | 0.0301      |
| CTA                             | 0.8960               | 0.5550        | 0.9120       | 0.6450      |
| TCA                             | 0.8800               | 0.2080        | 0.9020       | 0.3480      |
| CCA                             | 0.9750               | 0.7830        | 0.9810       | 0.8450      |
| ATP2C2: rs12448765-rs16963568-rs11645513
OMNIBUS                         | 0.0723               | NA            | 0.1260       |
| GCG                             | 0.8890               | 0.3950        | 0.8860       | 0.4170      |
| GAA                             | 0.9130               | 0.4210        | 0.9070       | 0.4240      |
| ACA                             | 1.3800               | 0.0108        | 1.3600       | 0.0227      |
| GCA                             | 0.9460               | 0.5310        | 0.9570       | 0.6400      |

P < 0.05 were indicated in bold. After Bonferroni correction, none of the associations highlighted in bold remained significant.

Supplement Table S3. However, none of these haplotypes survived Bonferroni correction for multiple comparisons.

In ATP2C2, rs2326254-rs4782946-rs8046864 (P = 0.0301, OR = 1.4000) and rs12448765-rs16963568-rs11645513 (P = 0.0227, OR = 1.3600) showed significant association with DD in TTC and ACA genotypes respectively (Table 3). Additionally, we also observed association of rs9929758-rs922450-rs1119141-rs34756715 (P = 0.0406, OR = 1.5400) and rs3743648-rs3743651-rs247808 (P = 0.0217, OR = 1.2900) in CCCT and CCG genotypes respectively (Supplement Table S4). However, none of these haplotypes remain significant after Bonferroni correction for multiple comparisons.

4. Discussion

To date, replication studies of CMIP and ATP2C2 with either SLI or DD mainly focused on seven SNPs of CMIP (rs12927866, rs4265801, rs7201632, rs6564903, rs3935802, rs16955705 and rs4243209) and six SNPs of ATP2C2 (rs8053211, rs11860694, rs16973771, rs2875891, rs8045507 and rs12149426) which were initially identified in British population (Newbury et al., 2009). Although some of above SNPs showed association with reading related traits in either SLI families or general population (Newbury et al., 2011; Scerri et al., 2011), case-control based association study of these SNPs in dyslexic families failed to demonstrate their association with DD (Newbury et al., 2011). Therefore, we expanded the coverage of CMIP and ATP2C2 through Tag SNP selection and performed high density genotyping in a large unrelated Chinese DD cohort. Indeed, we identified a number of SNPs in CMIP (Pmin = 0.0028) and ATP2C2 (Pmin = 0.0191) that showed association with DD though not survived Bonferroni correction for multiple comparisons. In addition, we found that some previously reported SNPs with SLI (Newbury et al., 2011) were not associated with DD. As such, rs12927866, rs16955705, rs6564903 of CMIP and rs16973771, rs2875891 of ATP2C2 failed to associate with DD in our cohort. To our knowledge, this study is the first association study of SLI candidate genes with DD in Chinese population.
Given the large number of Tag SNPs involved in association analysis, none of our results persisted significant after Bonferroni correction for multiple comparisons. We did realize that Bonferroni correction, as a Family-Wise Error Rate (FWER) based method, would yield a stringent significant threshold. Therefore we applied other FWER based methods including Holm, Hochberg and Hommel as well as False Discovery Rate (FDR) based methods including BH and BHY during data analysis. However, the results failed to survive any of these correction methods due to the large number of Tag SNPs in the present study. Based on our preliminary results, SLI candidate genes CMIP and ATP2C2 might not strongly associate with DD. Therefore, their pleiotropic effect underlying SLI and DD remains elusive (Newbury et al., 2011). To date, the genetic association of CMIP and ATP2C2 with DD has not been widely replicated across different populations. Therefore, their relevance to DD should be interpreted with caution.

In addition, it should be noted that Tag SNP is a genetic marker representing a cluster of SNPs in linkage disequilibrium therefore the causative variant might be hidden in the present study. As such, SNP imputation could be an option to estimate association of rest SNPs (Halperin & Stephan, 2009). However, evidence from functional investigation of CMIP and ATP2C2 during brain developmental and language processing would be rather direct and convincing. CMIP and ATP2C2 encode c-MAF inducing protein and calcium-transporting ATPase 2C2 respectively (Newbury et al., 2010). Both proteins showed expression in human brain but their functional consequence remains elusive. Furthermore, although CMIP and ATP2C2 located in the same SLI loci, they might contribute to DD through different mechanisms. Indeed, our ongoing studies are attempting to identify possible causative variants of CMIP and ATP2C2, and explicating their functional relevance to DD through further validations.

In conclusion, we performed association study of SLI candidate genes CMIP and ATP2C2 with DD in a large unrelated Chinese cohort through high density genotyping. We found nominal associations of CMIP and ATP2C2 with DD, though not survived Bonferroni correction for multiple comparisons. Based on our preliminary results, evidence supporting the association of CMIP and ATP2C2 with DD was weak. Currently, the relevance of CMIP and ATP2C2 to DD as well as the shared genetic etiology underlying DD and SLI should be interpreted with caution and worthwhile to be further characterized.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jneuroling.2014.06.005.

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