Replication of GWAS Loci Revealed an Increased Risk of BET1L and H19 Polymorphisms with Intracranial Aneurysm

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A genome-wide association study (GWAS) identified that BET1L rs2280543 at chromosome 11p15.5 was a susceptibility loci of intracranial aneurysm (IA). Long noncoding RNA H19, located in this region, was reported to play a crucial role in the formation of IA. In this study, we aimed to examine whether BET1L rs2280543 and potentially functional polymorphisms in H19 influence the risk of IA. A hospital-based case-control study was performed involving 542 IA patients and 588 age- and gender-matched controls. The BET1L rs2280543 CT, CT/TT genotypes, and T allele were associated with an increased risk of IA (CT vs. CC, adjusted OR = 1.43, 95% CI: 1.08-1.90, P = 0.01; CT/TT vs. CC, adjusted OR = 1.48, 95% CI: 1.12-1.94, P = 0.005; and T vs. C, adjusted OR = 1.44, 95% CI: 1.13-1.83, P = 0.003). Similarly, the H19 rs217727 TT genotype and T allele were associated with an increased risk of IA (TT vs. CC, adjusted OR = 1.90, 95% CI: 1.35-2.67, P < 0.001; T vs. C, adjusted OR = 1.38, 95% CI: 1.16-1.64, P < 0.001). Combined analyses revealed that the rs2280543 CC-rs217727 CT/TT, rs2280543 CT/TT-rs2735971 GG, and rs217727 CT/TT-rs2735971 GG genotypes were related to the risk of IA. Interaction analysis showed that the 3-loci model of rs2280543-rs217727-rs2839698 contributed to an increased risk of IA. These findings suggest that the GWAS-discovered risk loci BET1L rs2280543 may increase IA susceptibility by interacting with IncRNA H19.

1. Introduction

Intracranial aneurysm (IA) is a balloon-like dilation of the cerebral artery or vein, with an incidence rate of 2-3% in the general population [1]. Rupture of IA can cause 85% of subarachnoid hemorrhage, a death of approximately 50% of the cases, and a severe disability in 30% of the cases [2–4]. It is well accepted that lifestyle diseases including hypertension, cigarette smoking, excessive alcohol intake, and obesity are major risk factors for the development of IA [5–7]. Besides these factors, genetic factors are known to contribute to the physiopathology of IA [8, 9]. Approximately 20% of IA patients have a family history, and a 7-fold higher risk of IA was observed among first-degree relatives compared to second-degree relatives [8, 10–12]. Our previous work also identified some susceptibility loci for the development of IA, such as rs13293512 in the promoter of let-7 and rs4705342 in the promoter of miR-143/145 cluster [13, 14].

Previously, a genome-wide association study (GWAS) identified that 11p15.5 was a risk loci of IA, and a strong association of Bet1 Golgi vesicular membrane trafficking protein like (BET1L) rs2280543 at chromosome 11p15.5 with IA susceptibility was observed in a Japanese population [15]. However, little is known to date how the polymorphism influences IA development. Long noncoding RNAs (lnc RNAs), single-stranded noncoding RNAs of more than 200 nucleotides in length, were recently found to be implicated in many human diseases, including IA by regulating gene expression at the transcription level or posttranscription level [16–18]. Amounts of lncRNAs were reported to be aberrantly expressed in IA, including H19 [19, 20]. The lncRNA H19, imprinted maternally expressed transcript, is located at...
chromosome 11p15.5 that is the susceptibility loci of IA [15, 21]. Increasing evidence has shown that H19 is involved in the process of hypertension and atherosclerosis pathology [22–26], which are important risk factors for the development of IA [5–7].

Genetic variants in H19 have been demonstrated to play a key role in ischemic stroke [27] and coronary artery disease [28]. TT genotype of rs217727 in H19 was significantly associated with an increased risk of ischemic stroke, and the association remained after adjusting for confounding risk factors of stroke [27]. The increased risk of the rs217727 TT genotype in H19 was also observed in coronary artery disease [28]. However, no study to date has investigated the association between single-nucleotide polymorphisms (SNPs) in H19 and the risk of IA. In this work, a replication study of GWAS-discovered IA risk loci rs2280543 in BET1L was performed in a Chinese Han population. Moreover, the effect of potentially functional SNPs in H19 and their interaction with BET1L rs2280543 were also examined.

2. Materials and Methods

2.1. Ethics Statement. The case-control study was approved by the Institutional Review Board of the West China Hospital of Sichuan University, and written informed consent was provided by each participant. In cases with unconscious or illiterate patients, the written consent was completed by their relatives.

2.2. Study Population. The study subjects were enrolled from the West China Hospital of Sichuan University between January 2008 and July 2016, which included 542 IA patients and 588 controls. Detailed information of the study subjects was described previously [13, 14]. For the cases, peripheral blood samples were taken from patients who were definitely diagnosed with IA by digital subtraction angiography. Clinical information was also collected, including age, gender, systolic pressure, diastolic pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, the number of aneurysm, ruptured or unruptured aneurysm, and familial aneurysm or not. Patients who had hypertension, head trauma, intracranial atherosclerosis, and/or other nervous system diseases were excluded from the case group. Controls who came to the same hospital for a routine examination of physical condition at the same time period were selected. Controls with previous hypertension and/or some common nervous system diseases, such as stroke, traumatic brain injury, Alzheimer’s disease, and Parkinson’s disease, were excluded. All subjects were genetically unrelated Han Chinese living in Sichuan province or the surrounding area of southwest China.

2.3. SNP Selection. GWAS-identified risk loci BET1L rs2280543 was selected. Moreover, potentially functional SNPs in IncRNA H19 were selected if they met the following criteria: (a) minor allele frequency > 0.1 in the Chinese Han Beijing population of the 1000 Genomes Project and (b) in silico prediction of functional SNPs. Finally, 3 out of 12 SNPs in H19 were examined in this study since they have potential function, that is, the H19 rs217727 C allele influencing circulating concentrations of insulin-like growth factor 2 (IGF2) [29]; the rs2839698 CT and TT genotypes resulting in higher levels of H19 [30]; and the rs2735971 A/G having different binding affinity to transcriptional factor CCAAT/enhancer-binding protein alpha (C/EBPα).

2.4. Genotyping. Genomic DNA was extracted from peripheral blood leukocytes using the Biotek DNA isolation kit according to the manufacturer’s instructions (Biotek, Beijing, China). Genotyping analysis for the 4 SNPs was performed using the TaqMan allelic discrimination assay on an ABI 7900HT real-time PCR system (Applied Biosystems, CA, USA) [31, 32]. For quality control, the results were read by 2 research staff members blindly. Moreover, about 5% of the samples were selected for Sanger sequencing, and the concordance rates between duplicate samples were 100%.

2.5. Statistical Analysis. The SPSS software (version 19.0, SPSS Inc., Chicago, IL) was used for statistical analysis. Hardy-Weinberg equilibrium (HWE) was tested to compare the observed genotype distributions with the expected among controls using the $\chi^2$ test with one degree of freedom. The genotype frequencies of the 4 SNPs between IA cases and controls were compared using the $\chi^2$ test. Associations between the 4 SNPs and IA risk were evaluated by calculating odds ratios (ORs) and their 95% confidence intervals (CIs). ORs were adjusted by age, gender, and familial history of IA using the logistic regression analysis. In multiple comparisons, Bonferroni corrections were used to correct the alpha level of 0.0125 (0.05/4). Multifactor dimensionality reduction (MDR) analysis was carried out to assess BET1L-H19 interaction. All statistical tests were two-sided, and a $P$ value < 0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of the Study Population. The characteristics of the study population are summarized in Table 1. The mean age of the cases was 51.8 ± 11.8 years, and 39.3% of the patients were male. The mean age of the controls was 51.1 ± 9.1 years, and 36.9% of the controls were male. There was no significant difference between cases and controls according to age ($P = 0.26$) and gender ($P = 0.41$), indicating that the controls were frequency-matched to cases based on age and gender. Among the patients, 86.3% were diagnosed with single intracranial aneurysm, 88.0% with ruptured aneurysm, and 90.0% with nonfamilial aneurysm.

3.2. Association of the BET1L and H19 Polymorphisms with IA Risk. The association between the BET1L and H19 polymorphisms and IA risk was presented in Table 2. The genotype frequencies of the 4 SNPs in controls were in HWE ($P > 0.05$). For the BET1L rs2280543, an increased risk was significantly associated with the CT genotype (adjusted OR = 1.43, 95% CI: 1.08-1.90, $P = 0.01$) and the CT/TT genotypes (adjusted OR = 1.48, 95% CI: 1.12-1.94, $P = 0.005$) compared with the CC genotype. The similarly increased risk was also observed in the additive model.
Table 1: Demographics of controls and patients with IA.

|                                | Controls n = 588 | Patients with IA n = 542 | P value |
|--------------------------------|------------------|--------------------------|---------|
| Age (year, mean ± SD)          | 51.1 ± 9.1       | 51.8 ± 11.8              | 0.26    |
| Gender                         |                  |                          |         |
| Male                           | 217 (36.9)       | 213 (39.3)               | 0.41    |
| Female                         | 371 (63.1)       | 329 (60.7)               |         |
| Systolic pressure (mmHg, mean ± SD) | 109.1 ± 9.8     | 107.0 ± 12.9             | 0.25    |
| Diastolic pressure (mmHg, mean ± SD) | 76.5 ± 6.9     | 76.4 ± 6.2               | 0.90    |
| TC (mmol/L, mean ± SD)         | 4.4 ± 0.5        | 3.9 ± 0.4                | <0.001  |
| TG (mmol/L, mean ± SD)         | 1.2 ± 0.5        | 1.2 ± 0.3                | 0.07    |
| HDL-C (mmol/L, mean ± SD)      | 1.7 ± 0.8        | 1.4 ± 0.3                | <0.001  |
| LDL-C (mmol/L, mean ± SD)      | 2.1 ± 0.8        | 2.5 ± 0.7                | <0.001  |
| Multiple aneurysm              |                  |                          |         |
| Yes                            | 74 (13.7)        |                         |         |
| No                             | 468 (86.3)       |                         |         |
| Rupture of aneurysm            |                  |                          |         |
| Yes                            | 477 (88.0)       |                         |         |
| No                             | 65 (12.0)        |                         |         |
| Familial aneurysm              |                  |                          |         |
| Yes                            | 54 (10.0)        |                         |         |
| No                             | 488 (90.0)       |                         |         |

IA: intracranial aneurysm; SD: standard deviation; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

(adjusted OR = 1.40, 95% CI: 1.11-1.78, P = 0.005) and allele comparison (adjusted OR = 1.44, 95% CI: 1.13-1.83, P = 0.003). For the H19 rs217727, an increased risk was significantly associated with the TT genotype (adjusted OR = 1.90, 95% CI: 1.35-2.67, P < 0.001), T allele (adjusted OR = 1.38, 95% CI: 1.16-1.64, P < 0.001), and additive model (adjusted OR = 1.33, 95% CI: 1.13-1.56, P < 0.001). For the H19 rs2839698 and rs2735971, no significant difference of the genotype distributions was found between cases and controls. After stratification analyses according to the number of aneurysms and ruptured-versus-unruptured IA, we failed to find any association between the 4 SNPs and the clinical information (Tables 3 and 4).

3.3. Combined Analyses. Combined analyses revealed that individuals with the rs2280543 CC-rs217727 CT/TT genotypes had a 2.35-fold increased risk of IA compared to those with the rs2280543 CC-rs217727 CC genotypes (95% CI: 1.77-3.12, P < 0.001); individuals with the rs2280543 CT/TT-rs2735971 GG genotypes had a 1.63-fold increased risk of IA compared to those with the rs2280543 CC-rs2735971 GG genotypes (95% CI: 1.18-2.25, P = 0.003); and individuals with the rs217727 CT/TT-rs2735971 GG genotypes had a 1.46-fold increased risk of IA compared to those with the rs217727 CC-rs2735971 GG genotypes (95% CI: 1.09-1.95, P = 0.01) (Table 5).

3.4. Interaction Analysis. BET1L-H19 interaction analysis showed that the best candidate model was rs2280543-rs217727-rs2839698, with an accuracy of 0.65 and cross-validation consistency of 10/10 (OR = 3.36, 95% CI: 2.60-4.34, P < 0.001) (Table 6).

4. Discussion

In the present study, we examined whether BET1L and H19 polymorphisms were associated with the risk of IA. We found a statistically significant higher risk of BET1L rs2280543 CT, CT/TT genotypes, and T allele among IA patients. The increased risk of IA was also observed in individuals carrying the H19 rs217727 TT genotype and T allele. Combined analyses revealed that the rs2280543 CC-rs217727 CT/TT, rs2280543 CT/TT-rs2735971 GG, and rs217727 CT/TT-rs2735971 GG genotypes were related to the risk of IA. Interaction analysis showed that the 3-loci model of rs2280543-rs217727-rs2839698 contributed to an increased risk of IA.

Using the Quanto software, we computed the statistical power. Our study has more than 81% power if the OR was set at 1.7 under a dominant model. These findings suggest that the GWAS-discovered risk loci BET1L rs2280543 may increase IA susceptibility by interacting with lncRNA H19.

In 2012, Low et al. conducted a GWAS including 1383 IA patients and 5484 control individuals and identified a susceptibility loci BET1L rs2280543 at chromosome 11p15.5 in a Japanese population [15]. Further replication analysis using an additional set of 1048 IA cases and 7212 controls validated this result [15]. In this study, we selected 542 IA patients and 588 age- and gender-matched controls and found that the BET1L rs2280543 T variant increased the risk of IA in a Chinese population, which confirmed...
BET1L, encoded by BET1L gene, can facilitate the Golgi vesicular membrane trafficking process [33]. However, little is known to date of the biological function of BET1L in IA even though there is a previous report of rs2280543 in influencing BET1L expression levels in multiple human tissues [34].

The lncRNA H19, located on GWAS-discovered IA susceptibility loci of chromosome 11p15.5, was reported to be differentially expressed in IA [19, 20]. Silencing of H19 can inhibit proliferation and induce apoptosis of vascular smooth muscle cells by regulating the miR-148b/WNT/β-catenin pathway [26], whereas overexpression of H19 can promote proliferation and suppress apoptosis by regulating MAPK and NF-κB signaling pathway [23], implicating the important values of H19 in atherosclerosis and hypertension that are risk factors for the formation of IA [5–7]. With regard to the H19 polymorphisms in vascular diseases, Gao et al. reported that the H19 rs217727 T variant was associated with an increased risk of coronary artery disease in an additive model, dominant model, and recessive model, while the rs2067051 A variant was associated with a decreased risk of coronary artery disease in an additive model and recessive model [28]. Zhu et al. reported that the H19 rs217727 TT genotype was associated with an increased risk of ischemic stroke, especially in small vessel ischemic stroke [27]. Based on this background, we hypothesized that the BET1L rs2280543 may be involved in the occurrence of IA by interacting with lncRNA H19 polymorphisms. Our findings confirmed this hypothesis. We found that not only the H19 rs217727 TT genotype but also the combined genotypes of rs2280543 CC-rs217727 CT/TT and rs2280543 CT/TT-rs2735971 GG were associated with an increased risk of IA. Of note, we found that BET1L-H19 interaction (rs2280543-rs217727-rs2839698)
**Table 3: Stratification analyses by the number of aneurysms.**

| Polymorphisms | Multiple aneurysm, n = 74 (%) | Single aneurysm, n = 468 (%) | Adjusted OR (95%) | P value |
|---------------|-------------------------------|-------------------------------|-------------------|---------|
| **BET1L rs2280543** |                               |                               |                   |         |
| CC            | 59 (79.7)                     | 321 (68.6)                    | 1.00              |         |
| CT/TT         | 15 (20.3)                     | 147 (31.4)                    | 0.56 (0.31-1.02)  | 0.05    |
| C allele      | 130 (87.8)                    | 777 (83.0)                    | 1.00              |         |
| T allele      | 18 (12.2)                     | 159 (17.0)                    | 0.68 (0.40-1.14)  | 0.13    |
| **H19 rs217727** |                               |                               |                   |         |
| CC            | 20 (27.0)                     | 162 (34.6)                    | 1.00              |         |
| CT/TT         | 54 (73.0)                     | 306 (65.4)                    | 1.37 (0.79-2.38)  | 0.25    |
| C allele      | 72 (48.6)                     | 522 (55.8)                    | 1.00              |         |
| T allele      | 76 (51.4)                     | 414 (44.2)                    | 1.28 (0.91-1.82)  | 0.16    |
| **H19 rs2839698** |                               |                               |                   |         |
| CC            | 46 (62.2)                     | 266 (56.8)                    | 1.00              |         |
| CT/TT         | 28 (37.8)                     | 202 (43.2)                    | 0.79 (0.48-1.31)  | 0.36    |
| C allele      | 115 (77.7)                    | 703 (75.1)                    | 1.00              |         |
| T allele      | 33 (22.3)                     | 233 (24.9)                    | 0.85 (0.56-1.29)  | 0.45    |
| **H19 rs2735971** |                               |                               |                   |         |
| GG            | 53 (71.6)                     | 329 (70.3)                    | 1.00              |         |
| AG/AA         | 21 (28.4)                     | 139 (29.7)                    | 0.95 (0.55-1.64)  | 0.85    |
| G allele      | 123 (83.1)                    | 771 (82.4)                    | 1.00              |         |
| A allele      | 25 (16.9)                     | 165 (17.6)                    | 0.94 (0.59-1.49)  | 0.79    |

IA: intracranial aneurysm; OR: odds ratio; CI: confidence interval. †Adjusted by age, gender, and familial history of IA.

**Table 4: Stratification analyses by ruptured aneurysm (yes vs. no).**

| Polymorphisms | Ruptured aneurysm | Yes, n = 477 (%) | No, n = 65 (%) | Adjusted OR (95%) | P value |
|---------------|-------------------|-----------------|---------------|-------------------|---------|
| **BET1L rs2280543** |                   |                 |               |                   |         |
| CC            | 333 (69.8)        | 47 (72.3)       | 1.00          |                   |         |
| CT/TT         | 144 (30.2)        | 18 (27.7)       | 0.88 (0.49-1.56) | 0.65    |
| C allele      | 797 (83.5)        | 110 (84.6)      | 1.00          |                   |         |
| T allele      | 157 (16.5)        | 20 (15.4)       | 0.91 (0.55-1.52) | 0.72    |
| **H19 rs217727** |                   |                 |               |                   |         |
| CC            | 160 (33.5)        | 22 (33.8)       | 1.00          |                   |         |
| CT/TT         | 317 (66.5)        | 43 (66.2)       | 1.05 (0.60-1.82) | 0.87    |
| C allele      | 522 (54.7)        | 72 (55.4)       | 1.00          |                   |         |
| T allele      | 432 (45.3)        | 58 (44.6)       | 1.01 (0.70-1.47) | 0.94    |
| **H19 rs2839698** |                   |                 |               |                   |         |
| CC            | 270 (56.6)        | 42 (64.6)       | 1.00          |                   |         |
| CT/TT         | 207 (43.4)        | 23 (35.4)       | 0.71 (0.41-1.21) | 0.20    |
| C allele      | 714 (74.8)        | 104 (80.0)      | 1.00          |                   |         |
| T allele      | 240 (25.2)        | 26 (20.0)       | 0.74 (0.47-1.16) | 0.18    |
| **H19 rs2735971** |                   |                 |               |                   |         |
| GG            | 335 (70.2)        | 47 (72.3)       | 1.00          |                   |         |
| AG/AA         | 142 (29.8)        | 18 (27.7)       | 0.92 (0.51-1.64) | 0.77    |
| G allele      | 787 (82.5)        | 107 (82.3)      | 1.00          |                   |         |
| A allele      | 167 (17.5)        | 23 (17.7)       | 1.04 (0.64-1.68) | 0.88    |

IA: intracranial aneurysm; OR: odds ratio; CI: confidence interval. †Adjusted by age, gender, and familial history of IA.
conferred the risk of IA. These findings indicate that the BET1L rs2280543 increased IA risk partly by interacting with the lncRNA H19 polymorphisms.

We have to admit some limitations in this work. All individuals included in this study were Han Chinese, and thus, these findings cannot be directly extended to other ethnicities until confirmation results were obtained. Gene-gene and gene-environment interactions were important for an association study. BET1L-H19 interaction was performed in this study. However, gene-environment interaction cannot be assessed due to insufficient data. Control subjects were hospital-based and did not undergo magnetic resonance angiography screening. The possibility of selection bias therefore cannot be ruled out. Additionally, clinical information is incomplete, such as unavailable data of body mass index. Despite these limitations, replication analysis in this study verified the risk factor of BET1L rs2280543 in IA occurrence. Moreover, the lncRNA H19 may singly and interactively with BET1L contribute to the susceptibility of IA.

Table 5: Combined analyses of the BET1L and H19 polymorphisms with IA risk.

| Combined genotypes | Controls (%) | IA (%) | OR (95% CI) | P value |
|--------------------|--------------|--------|-------------|---------|
| rs2280543 CC-rs217727 CC | 238 (40.5) | 121 (22.3) | 1.00 |        |
| rs2280543 CC-rs217727 CT/TT | 217 (36.9) | 259 (47.8) | 2.35 (1.77-3.12) | <0.001 |
| rs2280543 CT/TT-rs217727 CC | — | 61 (11.3) | — | — |
| rs2280543 CT/TT-rs217727 CT/TT | 133 (22.6) | 101 (18.6) | 1.49 (1.06-2.10) | 0.02 |
| rs2280543 CC-rs2839698 CC | 237 (40.3) | 219 (40.4) | 1.00 |        |
| rs2280543 CC-rs2839698 CT/TT | 218 (37.1) | 161 (29.7) | 0.80 (0.61-1.05) | 0.11 |
| rs2280543 CT/TT-rs2839698 CC | 81 (13.8) | 93 (17.2) | 1.24 (0.88-1.76) | 0.22 |
| rs2280543 CT/TT-rs2839698 CT/TT | 52 (8.8) | 69 (12.7) | 1.44 (0.96-2.15) | 0.08 |
| rs2280543 CC-rs2735971 CC | 325 (55.3) | 265 (48.9) | 1.00 |        |
| rs2280543 CC-rs2735971 AG/AA | 130 (22.1) | 115 (21.2) | 1.09 (0.81-1.46) | 0.59 |
| rs2280543 CT/TT-rs2735971 GG | 88 (15.0) | 117 (21.6) | 1.63 (1.18-2.25) | 0.003 |
| rs2280543 CT/TT-rs2735971 AG/AA | 45 (7.7) | 45 (8.3) | 1.23 (0.79-1.91) | 0.37 |

Table 6: Interaction analysis of the BET1L and H19 polymorphisms and risk of IA.

| Best candidate models | Accuracy | Cross-validation consistency | OR (95% CI) | P value |
|----------------------|----------|-------------------------------|-------------|---------|
| rs217727 CC-rs2839698 CC | 128 (21.8) | 105 (19.4) | 1.00 |        |
| rs217727 CC-rs2839698 CT/TT | 110 (18.7) | 77 (14.2) | 0.85 (0.58-1.26) | 0.42 |
| rs217727 CT/TT-rs2839698 CC | 190 (32.3) | 207 (38.2) | 1.33 (0.96-1.84) | 0.09 |
| rs217727 CT/TT-rs2839698 CT/TT | 160 (27.2) | 153 (28.2) | 1.17 (0.83-1.64) | 0.38 |
| rs217727 CC-rs2735971 GG | 175 (29.8) | 128 (23.6) | 1.00 |        |
| rs217727 CC-rs2735971 AG/AA | 63 (10.7) | 54 (10.0) | 1.17 (0.76-1.80) | 0.47 |
| rs217727 CT/TT-rs2735971 GG | 238 (40.5) | 254 (46.9) | 1.46 (1.09-1.95) | 0.01 |
| rs217727 CT/TT-rs2735971 AG/AA | 112 (19.0) | 106 (19.6) | 1.29 (0.91-1.84) | 0.15 |

IA: intracranial aneurysm; OR: odds ratio; CI: confidence interval.

Data Availability

All data included in this study are available upon request by contact with the corresponding author.
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