Positive Association between ANKRD55 Polymorphism 7731626 and Dermatomyositis/Polymyositis with Interstitial Lung Disease in Chinese Han Population

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1. Introduction

Dermatomyositis (DM) and polymyositis (PM) are autoimmune diseases that are most prevalent in women and the elderly [1], characterized by the shared features of skeletal muscle weakness, elevated serum creatine kinase levels, and inflammation in muscle biopsy [2, 3]. It has been reported that DM/PM prevalence ranges from 21.42 to 32.74/100,000 person-years (py) in the USA [1, 4, 5] and from 10 to 13/100,000 py in Japan with an increasing trend [6]. Though DM/PM most frequently affects the skin and muscles, it may also affect multiple organs, most notably, the lung. Interstitial lung disease (ILD) is the primary pulmonary manifestation, which is associated with a high morbidity and mortality in DM/PM patients [7–9]. It would, therefore, be advantageous to investigate the biomarkers associated with the development of ILD in patients with DM/PM. To date, several genetic [10–12] and environmental [13–16] factors have been proposed to contribute to the development of DM/PM. However, these identified predisposing factors are unable to completely account for the pathogenesis of DM/PM.

Studies have reported that autoimmune diseases share a number of human leukocyte antigen (HLA) and non-HLA genes [12, 17–19]. A genome-wide association study (GWAS) revealed DM shares genetic susceptibility factors with
rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), and other autoimmune diseases [12]. Recent studies identified that single nucleotide polymorphisms (SNPs) of TNFSF4 (rs2205960, rs844644, and rs844648) and ANKRD55 (rs6859219, rs7731626) also shared susceptibility loci for RA [20-22], MS [17], and SLE [23, 24]. The association of the five SNPs with the diseases discussed is summarized in Table S1 (see Table S1 in the Supplementary Material available online at https://doi.org/10.1155/2017/2905987). TNFSF4 encodes the ligand for TNFRSF4, and this receptor-ligand pair can activate CD4+ T cells [25]. The TNFSF4-TNFRSF4 interaction has been shown to contribute to the induction of antitumor immunity [26] and the inhibition of allergic responses [27, 28]. ANKRD55 encodes ankyrin repeat domain-containing protein 55, which mediates protein-protein interactions. A recent report has revealed that ANKRD55 can be detected in resting CD4+ T cells and monocytes and may have possible relevance to autoimmune diseases (http://www.amazonia.transcriptome.eu) [29]. However, the exact function of ANKRD55 remains unknown. In order to elucidate whether the five genetic polymorphisms of TNFSF4 and ANKRD55 are associated with DM/PM in a Chinese Han population, we performed the current study including 1017 DM/PM patients and 1280 matched healthy controls.

2. Materials and Methods

2.1. Subjects. The current study was a multicenter case-control study, approved by the Ethics Committee of the Peking Union Medical College Hospital, China. Patients with DM/PM fulfilled the Bohan and Peter criteria [30] and were recruited between February 2013 and June 2015. A total of 1017 DM/PM patients including 569 patients from the Peking Union Medical College Hospital, along with 448 patients from another 21 centers in China, were enrolled. The sera from 659 recruited patients were analyzed for anti-Jo-1 antibody using QUANTA Lite Jo-1-ELISA assay (Inova Diagnostics, San Diego, CA, USA). Patients with ILD were identified with high-resolution chest computed tomography (HRCT). In addition, 1280 gender-matched healthy individuals from the Peking Union Medical College Hospital were recruited in this study. 287 DM/PM patients from Peking Union Medical College Hospital were followed up for 3 yrs. All participants were from the Chinese Han population and provided signed informed consent.

2.2. Genotyping. We collected 2 ml peripheral blood from each participant in an ethylenediaminetetraacetic acid (EDTA-) coated tube. DNA was extracted from peripheral white blood cell using genomic DNA kits (Tiangen, Beijing, China) and stored at −80°C until use. The genotyping of the five SNPs from TNFSF4 and ANKRD55 genes was performed using Sequenom MassArray system (San Diego, CA, USA) according to the manufacturer’s protocol. Primers for polymerase chain reaction (PCR) and locus-specific single-base extension were designed by MassArray Assay Design 4.0 (Sequenom). Briefly, all DNA samples were transferred to a 384-well plate. After multiplex PCR amplifications, the products were used for locus-specific single-base extension reaction. Afterwards, the products were desalted and transferred onto a 384-element SpectroCHIParray (Sequenom). Allele detection was conducted by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS). Finally, MassArrayTyper 4.0 software was used to analyze the resultant mass spectrometry and genotype data.

2.3. Statistical Analysis. The Chi-square ($\chi^2$) test was used to assess whether each SNP in the control populations conformed to Hardy-Weinberg equilibrium (HWE). Any SNPs that deviated from the HWE ($P < 0.05$ in the controls) would be excluded in the analysis. The differences in allelic and genotypic frequencies between patients and controls were calculated by $\chi^2$ test. The risk allele frequency for each SNP between DM/PM patients with ILD and controls was calculated. The odds ratio (OR) and 95% confidence interval (95% CI) of the association were calculated; $P$ values $< 0.05$ (adjusted by Bonferroni correction) were considered to be statistically significant. The logistic regression models (additive, dominant, and recessive models) were used to further analyze the genotype frequencies. For the association analysis between the five SNPs and the three subsets (DM, PM, or overall DM/PM versus controls), statistical analysis was performed using PLINK v1.07 (Shaun Purcell, Boston, MA, USA) [31]. The association study for the five SNPs and the presence of ILD were performed according to the results of the following comparisons: patients with ILD versus patients without ILD, patients with ILD versus controls, and patients without ILD versus controls.

3. Results

3.1. Clinical Characteristics of Participants. The demographics and clinical features of enrolled DM/PM patients and healthy controls were displayed in Table 1. A total of 1017 DM/PM patients (25.7% male, 74.3% female; mean age 46.1±15.2) were recruited, including 654 DM patients and 363 PM patients. Among these patients, 390 of 654 patients had DM and 195 of 363 patients had PM complicated by ILD. In total, 585 of 1017 patients had DM/PM complicated by ILD, while 432 did not. Of 659 DM/PM patients who were assessed for anti-Jo-1 antibody, 115 patients (61 DM patients and 54 PM patients) were positive for anti-Jo-1 antibody. During the 3-year follow-up, 14 DM/PM patients developed new malignant tumors, including six patients with lung cancer, three with breast cancer, two with ovarian cancer, one with liver cancer, one with nasopharynx cancer, and one with synovial sarcoma. The analysis of the five selected SNPs is shown in Table 2. All SNPs had call rates > 99% and followed HWE in the controls ($P_c > 0.05$, Table 2).

3.2. Association of the Five SNPs with DM, PM, or DM/PM in the Han Population. Five SNPs rs2205960, rs844644, rs844648, rs6859219, and rs7731626 were genotyped in 1017 DM/PM patients (DM, $n = 654$; PM, $n = 363$) and
Table 1: Clinical features of DM/PM patients and healthy controls.

|                        | Cases                   | Controls                  |
|------------------------|-------------------------|---------------------------|
|                        | Number/total            | %                         | Number/total            | %                         |
| **Mean age**           | 46.1 ± 15.2             |                           | 41.8 ± 12.7             |                           |
| **Male**               | 261/1017                | 25.7                      | 165/1280                | 12.9                      |
| **Female**             | 756/1017                | 74.3                      | 1115/1280               | 87.1                      |
| **DM**                 | 654/1017                | 64.3                      |                           |                           |
| **PM**                 | 363/1017                | 35.7                      |                           |                           |
| **ILD**                | 585/1017                | 57.5                      |                           |                           |
| **DM with ILD**        | 390/1017                | 38.3                      |                           |                           |
| **PM with ILD**        | 195/1017                | 19.2                      |                           |                           |
| **Anti-Jo-1 antibody** | 115/659                 | 17.5                      |                           |                           |
| **DM with anti-Jo-1 antibody** | 61/438 | 13.9                      |                           |                           |
| **PM with anti-Jo-1 antibody** | 54/221 | 24.4                      |                           |                           |
| **Malignancy**         | 14/287                  | 4.9                       |                           |                           |
| **Lung cancer**        | 6/14                    | 42.9                      |                           |                           |
| **Breast cancer**      | 3/14                    | 21.4                      |                           |                           |
| **Ovarian cancer**     | 2/14                    | 14.3                      |                           |                           |
| **Liver cancer**       | 1/14                    | 7.1                       |                           |                           |
| **Nasopharynx cancer** | 1/14                    | 7.1                       |                           |                           |
| **Synovial sarcoma**   | 1/14                    | 7.1                       |                           |                           |

DM = dermatomyositis; PM = polymyositis; ILD = interstitial lung disease.

Table 2: The information of five selected SNPs.

| Gene    | SNP          | Chromosome | Position     | Function class | Allele | MAF in CHB (dbSNP) | MAF | \(P_c\) for HWE Call rate (\%) |
|---------|--------------|------------|--------------|----------------|--------|--------------------|-----|-----------------------------|
| TNFSF4  | rs2205960    | 1          | 173222336    | NA             | G > T  | 0.198              | 0.265 | 0.655 | 100                        |
| TNFSF4  | rs844644     | 1          | 173240356    | Intron         | A > C  | 0.384              | 0.445 | NS   | 99.96                      |
| TNFSF4  | rs844648     | 1          | 173254724    | Intron         | G > A  | 0.384              | 0.453 | NS   | 100                        |
| ANKRDS5 | rs6859219    | 5          | 56142753     | Intron         | C > A  | 0.012              | 0.005 | NS   | 100                        |
| ANKRDS5 | rs7731626    | 5          | 56148856     | Intron         | G > A  | NA                 | 0.089 | NS   | 100                        |

The information was gathered from dbSNP database in NCBI. SNPs = single nucleotide polymorphisms; MAF = minor allele frequency; CHB = Han Chinese in Beijing, China; \(P_c\) = \(P\) value corrected by Bonferroni method; HWE = Hardy-Weinberg equilibrium; NA = not available; NS = not significant.

**3.3. Association between the Five SNPs and ILD Phenotype of DM/PM.** To analyze the association between the five SNPs and ILD phenotype of DM/PM patients, the five SNPs of TNFSF4 and ANKRDS5 were genotyped in 585 DM/PM patients with ILD (DM-ILD, \(n = 390\); PM-ILD, \(n = 195\)). A significantly decreased frequency of SNP rs7731626-A was observed in DM-ILD (6.54% in DM-ILD, 9.77% in the controls, \(P_c = 0.030\), OR = 0.65, 95% CI: 0.47–0.88, Table 5) and DM/PM-ILD patients (6.75% versus 9.77%, \(P_c = 0.015\), OR = 0.67, 95% CI: 0.51–0.87, Table 5) as compared to healthy controls. No significant association was observed between SNP rs7731626-A and PM patients with ILD. The clinical significance of SNP rs7731626-A for DM-ILD and DM/PM-ILD still needs further study. In addition, no significant association was detected between the other four SNPs and patients with ILD or without ILD when comparing patients with ILD versus patients without ILD, patients with ILD versus controls, or patients without ILD versus controls (\(P_c > 0.05\), Table 5).

**4. Discussion**

In this multiple-center, large-sample case-control study, we investigated the associations of TNFSF4 (rs2205960, rs844644, and rs844648) and ANKRDS5 (rs6859219, rs7731626) polymorphisms with the susceptibility to DM/PM in a Chinese Han population. Our results demonstrated that ANKRDS5' polymorphism (rs7731626) was significantly associated with DM-ILD as well as DM/PM-ILD. A significant decrease in the frequency of rs7731626-A allele in
Table 3: Allele and genotype frequencies of the five SNPs in DM/PM patients and healthy controls.

| Gene  | SNP         | Groups   | Allele (%) | OR (95% CI) | $P_c$ | Genotype (%) | $\chi^2$ | $P_c$ |
|-------|-------------|----------|------------|-------------|-------|--------------|----------|-------|
|       |             |          | T          | G           |       |              |          |       |
|       |             | DM       | 344 (26.30) | 964 (73.70) | 1.00 (0.86–1.16) | NS | 43 (6.57) | 258 (39.43) | 353 (53.98) | 0.30 | NS |
|       |             | PM       | 197 (27.13) | 529 (72.87) | 1.04 (0.87–1.26) | NS | 21 (5.79) | 155 (42.70) | 187 (51.52) | 0.59 | NS |
|       |             | DM/PM    | 541 (26.60) | 1493 (73.40) | 1.01 (0.89–1.16) | NS | 64 (6.29) | 413 (40.61) | 540 (53.10) | 0.05 | NS |
|       |             | Controls | 674 (26.33) | 1886 (73.67) | 1.00 (0.86–1.16) | NS | 78 (6.09) | 518 (40.47) | 684 (53.44) |       |     |
|       |             |          | C          | A           |       |              |          |       |
|       |             | DM       | 601 (45.95) | 707 (54.05) | 1.10 (0.96–1.26) | 0.850 | 129 (19.72) | 343 (52.45) | 182 (27.83) | 3.17 | NS |
|       |             | PM       | 325 (44.77) | 401 (55.23) | 1.05 (0.89–1.24) | NS | 67 (18.46) | 191 (52.62) | 105 (28.92) | 1.40 | NS |
|       |             | DM/PM    | 926 (45.53) | 1108 (54.47) | 1.08 (0.96–1.21) | 0.995 | 196 (19.27) | 534 (52.51) | 287 (28.22) | 3.53 | 0.855 |
|       |             | Controls | 1116 (43.63) | 1442 (56.37) | 1.00 (0.87–1.20) | NS | 243 (19.00) | 630 (49.26) | 406 (31.74) |       |     |
|       |             |          | A          | G           |       |              |          |       |
|       |             | DM       | 607 (46.41) | 701 (53.59) | 1.08 (0.94–1.23) | NS | 129 (19.72) | 349 (53.36) | 176 (26.91) | 5.53 | 0.315 |
|       |             | PM       | 332 (45.73) | 394 (54.27) | 1.05 (0.89–1.24) | NS | 68 (18.73) | 196 (53.99) | 99 (27.27) | 0.14 | 0.655 |
|       |             | DM/PM    | 939 (46.17) | 1095 (53.83) | 1.07 (0.95–1.20) | NS | 197 (19.37) | 545 (53.59) | 275 (27.04) | 7.50 | 0.115 |
|       |             | Controls | 1141 (44.57) | 1419 (55.43) | 1.00 (0.87–1.20) | NS | 263 (20.55) | 615 (48.05) | 402 (31.41) |       |     |
|       |             |          | A          | C           |       |              |          |       |
|       |             | DM       | 5 (0.38) | 1303 (99.62) | 0.75 (0.27–2.11) | NS | 0 (0.00) | 5 (0.76) | 649 (99.24) | NA | NA |
|       |             | PM       | 5 (0.69) | 721 (99.31) | 1.36 (0.48–3.82) | NS | 0 (0.00) | 5 (1.38) | 358 (98.62) | NA | NA |
|       |             | DM/PM    | 10 (0.49) | 2024 (99.51) | 0.97 (0.42–2.21) | NS | 0 (0.00) | 10 (0.98) | 1007 (99.02) | NA | NA |
|       |             | Controls | 13 (0.51) | 2547 (99.49) | 1.00 (1.00–1.00) | NS | 0 (0.00) | 13 (1.02) | 1267 (98.98) |       |     |
|       |             |          | A          | G           |       |              |          |       |
|       |             | DM       | 99 (7.57) | 1209 (92.43) | 0.76 (0.59–0.96) | 0.120 | 5 (0.76) | 89 (13.61) | 560 (85.63) | 4.93 | 0.425 |
|       |             | PM       | 58 (79.99) | 668 (20.01) | 0.80 (0.60–1.08) | 0.735 | 1 (0.28) | 56 (15.43) | 306 (84.30) | NA | NA |
|       |             | DM/PM    | 157 (7.72) | 1877 (92.28) | 0.77 (0.63–0.95) | 0.075 | 6 (0.59) | 145 (14.26) | 866 (85.15) | 6.14 | 0.23 |
|       |             | Controls | 250 (9.27) | 2310 (90.23) | 1.00 (1.00–1.00) | NS | 16 (1.25) | 218 (17.03) | 1046 (81.72) |       |     |

SNPs = single nucleotide polymorphisms; DM = dermatomyositis; PM = polymyositis; OR = odds ratio; CI = confidence interval; $P_{c}$ = $P$ value corrected by Bonferroni method; $\chi^2$ = Chi-square test; NS = not significant; NA = not available.
| Gene      | SNP       | Allele | Group         | Additive model | Dominant model | Recessive model |
|-----------|-----------|--------|---------------|----------------|----------------|----------------|
|           |           |        |               | \( P_c \)      | \( P_c \)      | \( P_c \)      |
|           |           |        |               | OR (95% CI)    | OR (95% CI)    | OR (95% CI)    |
| TNFSF4    | rs2205960 | T      | DM            | NS             | 1.00 (0.86–1.17) | NS             | 0.98 (0.81–1.18) | NS             | 1.09 (0.74–1.59) |
|           |           |        | PM            | NS             | 1.04 (0.86–1.26) | NS             | 1.08 (0.86–1.36) | NS             | 1.09 (0.74–1.59) |
|           |           |        | DM/PM         | NS             | 1.02 (0.89–1.16) | NS             | 1.01 (0.86–1.20) | NS             | 1.04 (0.74–1.46) |
| TNFSF4    | rs844644  | C      | DM            | 0.830          | 1.10 (0.96–1.26) | 0.385          | 1.21 (0.98–1.48) | NS             | 1.05 (0.83–1.33) |
|           |           |        | PM            | NS             | 1.05 (0.89–1.24) | NS             | 1.14 (0.89–1.48) | NS             | 1.05 (0.83–1.33) |
|           |           |        | DM/PM         | 0.965          | 1.08 (0.96–1.22) | 0.340          | 1.18 (0.99–1.42) | NS             | 1.02 (0.83–1.26) |
| TNFSF4    | rs844648  | A      | DM            | NS             | 1.08 (0.94–1.23) | 0.205          | 1.24 (1.01–1.53) | NS             | 0.95 (0.75–1.20) |
|           |           |        | PM            | 1.05 (0.89–1.24) | 0.655          | 1.22 (0.94–1.58) | NS             | 0.95 (0.75–1.20) |
|           |           |        | DM/PM         | 1.07 (0.95–1.20) | 0.115          | 1.24 (1.03–1.48) | NS             | 0.93 (0.76–1.14) |
| ANKRD55   | rs6859219 | A      | DM            | NS             | 0.75 (0.27–2.12) | NS             | 0.75 (0.27–2.12) | NA             | NA             |
|           |           |        | PM            | NS             | 1.36 (0.48–3.84) | NS             | 1.36 (0.48–3.84) | NA             | NA             |
|           |           |        | DM/PM         | NS             | 0.97 (0.42–2.22) | NS             | 0.97 (0.42–2.22) | NA             | NA             |
| ANKRD55   | rs7731626 | A      | DM            | 0.135          | 0.76 (0.60–0.97) | 0.155          | 0.75 (0.58–0.97) | NS             | 0.61 (0.22–1.67) |
|           |           |        | PM            | 0.760          | 0.81 (0.60–1.08) | NS             | 0.83 (0.64–1.14) | 0.700          | 0.61 (0.22–1.67) |
|           |           |        | DM/PM         | 0.085          | 0.78 (0.63–0.96) | 0.145          | 0.78 (0.62–0.97) | 0.575          | 0.47 (0.18–1.20) |

SNPs = single nucleotide polymorphisms; \( P_c \) = \( P \) value corrected by Bonferroni method; OR = odds ratio; CI = confidence interval; DM = dermatomyositis; PM = polymyositis; NS = not significant; NA = not available.
Table 5: Association of the five SNPs and DM/PM patients with ILD.

| Disease | Group   | rs2205960 (TNFSF4) | rs844644 (TNFSF4) | rs844648 (TNFSF4) | rs6859219 (ANKRD55) | rs7731626 (ANKRD55) |
|---------|---------|--------------------|-------------------|-------------------|--------------------|--------------------|
|         |         | Risk allele T (%)  | OR (95% CI)       | Risk allele C (%)  | OR (95% CI)       | Risk allele A (%)  | OR (95% CI)       | Risk allele A (%)  | OR (95% CI)       | Risk allele A (%)  | OR (95% CI)       |
| DM      | P versus N 24.49 versus 28.98 | 0.350 | 0.79 (0.62–1.02) | 45.38 versus 46.78 | NS                  | 0.95 (0.76–1.18) | 46.41 versus 46.40 | NS                  | 0.51 versus 0.19 | 0.79 (0.62–1.02) | 6.54 versus 0.435 | 0.70 (0.46–1.06) |
|         | P versus C 24.49 versus 26.33 | NS    | 0.91 (0.75–1.09) | 45.38 versus 43.63 | NS                  | 1.07 (0.91–1.26) | 46.41 versus 44.57 | NS                  | 0.51 versus 0.51 | 0.95 (0.76–1.18) | 6.54 versus 0.030 | 0.65 (0.47–0.88) |
|         | N versus C 28.98 versus 26.33 | NS    | 1.14 (0.93–1.41) | 46.78 versus 43.63 | 0.920               | 1.14 (0.94–1.37) | 46.40 versus 44.57 | NS                  | 0.19 versus 0.37 | 0.95 (0.76–1.18) | 9.09 versus 0.92 (0.67–1.28) |
| PM      | P versus N 2718 versus 2708 | NS    | 1.01 (0.72–1.40) | 45.64 versus 43.75 | NS                  | 1.08 (0.80–1.45) | 46.92 versus 44.35 | NS                  | 0.51 versus 0.89 | 0.57 (0.40–1.54) | 6.71 versus 0.79 | 0.46–1.35 |
|         | P versus C 2718 versus 26.33 | NS    | 1.04 (0.82–1.33) | 45.64 versus 43.63 | NS                  | 1.09 (0.88–1.34) | 46.92 versus 44.57 | NS                  | 0.51 versus 0.51 | 0.95 (0.76–1.18) | 7.18 versus 9.77 | 0.48–1.07 |
|         | N versus C 2708 versus 26.33 | NS    | 1.04 (0.80–1.34) | 43.75 versus 43.63 | NS                  | 1.01 (0.79–1.32) | 44.35 versus 44.57 | NS                  | 0.89 versus 1.77 | 0.95 (0.76–1.18) | 8.93 versus 9.77 | 0.91 |
| DM/PM   | P versus N 25.38 versus 28.24 | 0.750 | 0.86 (0.71–1.05) | 45.47 versus 45.60 | NS                  | 0.99 (0.83–1.19) | 46.58 versus 45.60 | NS                  | 0.51 versus 0.46 | 1.11 (0.87–1.42) | 6.75 versus 0.285 | 0.73 (0.53–1.01) |
|         | P versus C 25.38 versus 26.33 | NS    | 0.95 (0.81–1.12) | 45.47 versus 43.63 | NS                  | 1.08 (0.94–1.24) | 45.68 versus 44.57 | NS                  | 0.51 versus 0.51 | 1.01 (0.87–1.24) | 6.75 versus 0.015 | 0.67 (0.51–0.87) |
|         | N versus C 28.24 versus 26.33 | NS    | 1.10 (0.93–1.31) | 43.63 versus 43.63 | NS                  | 1.08 (0.93–1.27) | 45.60 versus 44.57 | NS                  | 0.46 versus 0.51 | 0.91 (0.80–1.20) | 9.03 versus 9.77 | 0.70–1.20 |

Bold values indicate statistical significance (\(P_c < 0.05\); SNPs = single nucleotide polymorphisms; DM = dermatomyositis; PM = polymyositis; ILD = interstitial lung disease; \(P_c\) = \(P\) value corrected by Bonferroni method; OR = odds ratio; CI = confidence interval; Group P: patients with ILD; Group N: patients without ILD; Group C: healthy controls; Group P (DM: \(n = 390\); PM: \(n = 195\); DM/PM: \(n = 585\)); Group N (DM: \(n = 264\); PM: \(n = 168\); DM/PM: \(n = 432\)); Group C (\(n = 1280\)).
DM-ILD and DM/PM-ILD patients compared to controls may suggest that this allele may play a protective role against the development of ILD. Notably, this was the first study to demonstrate that the ANKRD55 polymorphism was associated with Chinese DM/PM patients with ILD.

ILD is a common complication of DM/PM and progression of ILD is a leading cause of mortality [7–9]. Several gene polymorphisms have been revealed to be associated with DM/PM patients with ILD, including STAT4 rs7574865 polymorphism [32] and TNFAIP3 rs2230926 and rs5029939 polymorphisms [33]. However, these identified susceptibility genes do not fully account for the genetic pathogenesis of DM/PM-ILD. ANKRD55 has been shown to be inducible following inflammatory stimuli, and its expression may also increase susceptibility to inflammation in patients [29]. An increase in the protein expression of ANKRD55 in autoimmune encephalomyelitis mice suggests that this molecule may act as a disease biomarker. Although the precise function of ANKRD55 is still unknown, a link between genetic variants of ANKRD55 and autoimmune diseases may exist. At loci ANKRD55, rs7731626 is located in immune cell enhancer regions [34]. To date, few studies have examined the association of SNP rs7731626 of ANKRD55 with different diseases. Okada et al. reported that rs7731626-G was a risk factor for the development of RA by comparing 12,841 RA patients with 33,416 healthy controls in a European population [20]. In our presented study, our data demonstrated rs7731626 was negatively associated with DM-ILD and DM/PM-ILD in Chinese Han patients, whereby the protective A allele was the minor allele in these patients. Our results indicated that DM/PM-ILD may share a common genetic locus with RA. However, no association was found between DM/PM and SNP rs6859219 of ANKRD55, which has been shown to be related to MS [37, 35] and RA [21, 22] (Table S1).

TNFSF4 with its receptor TNFRSF4 promotes CD4+ T cells activation as a potent costimulatory signal [36]. Recent studies have demonstrated that polymorphisms of TNFSF4 (rs2205960, rs844644, and rs844648) are associated with SLE [23, 24, 37, 38] and systemic sclerosis (SSc) [39] (Table S1). To explore whether SNPs rs2205960, rs844644, and rs844648 are also associated with DM/PM, we conducted the present study. Our data showed no statistically significant association existed between TNFSF4 polymorphisms and DM/PM, suggesting the pathogenesis of DM/PM may differ from SLE and SSc. Additional studies in different ethnic groups should be performed in the future to further investigate the association of rs2205960, rs844644, and rs844648 with DM/PM.

There are, however, some limitations to our study. The current case-control study revealed that the minor allele (A) of rs7731626 was less frequent in DM-ILD and DM/PM-ILD than in controls (Table 5). We hypothesize that the A variant may be protective for DM-ILD. However, in order to decide if this result is robust enough to also be clinically significant, multiple studies with different sample sizes are needed in the future study. Whether this variant affects the properties of ANKRD55 protein in a way which is compatible with this hypothesis requires further confirmation. In addition, we only investigated the association of rs7731626 with DM-ILD or DM/PM-ILD in the Han Chinese population. Due to ethnic genetic differences, further investigations are required to confirm the association of ANKRD55 genetic variants with DM-ILD or DM/PM-ILD in Caucasian and African patients.

5. Conclusions

This study was the first study to elucidate that a rare variant within the ANKRD55 gene (rs7731626) is protective in DM-ILD and DM/PM-ILD in a Chinese Han population. Further studies are needed to investigate the association of ANKRD55 genetic variants with DM-ILD or DM/PM-ILD in different ethnic groups from variable geographical regions.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

Liubing Li, Si Chen, and Xiaoting Wen contributed equally to this manuscript.

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