To the Editor: Pulmonary arterial hypertension (PAH) is a hemodynamic disorder with elevated pressure of pulmonary circulation. Genetic studies in familial PAH (fPAH) and idiopathic PAH (iPAH) have discovered that transforming growth factor-β (TGF-β) superfamily plays an important role, and the identified mutations occur in bone morphogenetic protein type 2 receptor (BMPR2), activin receptor-like kinase type 1 (ALK1), Endoglin, and SMAD9[1]. A genome-wide association study (GWAS) in patients without BMPR2 mutations discovered that one single-nucleotide polymorphism (SNP) rs2217560 had a significant association with iPAH, which located 52-kb downstream of the CBLN2 gene.[2] A major cause of PAH is connective tissue diseases (CTDs), including systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Even though CTD-associated PAH (CTD-PAH) constitutes 25% of PAH cases, little has been done on related genetic study. SSc-associated PAH (SSc-PAH) has higher occurrence in Western countries, while in China, SLE-PAH consists over 50% of CTD-PAH.[3] Nearly 4% of lupus patients suffer from PAH, and PAH is one of the leading causes of death for SLE.[4] We conducted this research to explore the genetic susceptibility of PAH in SLE.

Totally 87 SLE-PAH patients were included based on a clinical registry in Peking Union Medical College Hospital, China.[5] PAH was diagnosed by right heart catheterization. About 96.3% of the patients are female. The average age is 34.4 ± 8.1 years. SLE-PAH patients present with mean pulmonary arterial pressure, 46 mmHg; pulmonary vascular resistance, 10 wood units; and mean pulmonary arterial pressure, 25% of PAH cases, little has been done on related genetic study. SSc-associated PAH (SSc-PAH) has higher occurrence in Western countries, while in China, SLE-PAH consists over 50% of CTD-PAH.[3] Nearly 4% of lupus patients suffer from PAH, and PAH is one of the leading causes of death for SLE.[4] We conducted this research to explore the genetic susceptibility of PAH in SLE.

In our study, there was a difference between the frequency of allele in SLE-PAH patients compared with SLE-non-PAH group (9% vs. 6.1%); however, it was not statistically significant (χ² = 0.343–42.388, P = 0.275). The association between SNP allelic/genotypic frequencies and disease onset was listed in Table 1.

Rs2217560 (G>A) lies 52-kb downstream of the CBLN2 gene, within the transcriptional regulatory region. Rs2217560 G-allele was more frequent in SLE-PAH group than in SLE-non-PAH group (27% vs. 20%; genotypic frequency of GG/GA/AA was 4/36/41 versus 10/37/94 and was statistically significant (χ² = 7.742, P = 0.021). Dominant and additive hereditary models were further tested for rs2217560, and G-allele was found associated with PAH onset with odds ratio (OR) of 1.951 in dominant model (95% confidence interval [CI] = 1.116–3.412, P = 0.019).

Rs2277382 (G>T) is located in 5'-UTR of ALK1 gene. In a previous small-scale study in SSc-PAH patients, rs2277382 was detected only in SSc-PAH patients, but replication set did not prove association with SSc-PAH.[6] In our study, there was a difference between the frequency of allele in SLE-PAH patients compared with SLE-non-PAH patients (9% vs. 6.1%); however, it was not statistically significant (OR = 1.542, 95% CI = 0.762–3.121, P = 0.228).

Rs34135567 is a deletion/C/A variation in 3'-UTR of BMPR2. There was no statistical association with PAH onset (OR = 3.815, 95% CI = 0.343–42.388, P = 0.276; χ² = 1.381, P = 0.275).

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Table 1: Association between SNP allelic/genotypic frequencies and disease onset

| Rs     | Group | Allele | OR       | P       | Genotype | χ²   | P       |
|--------|-------|--------|----------|---------|----------|------|---------|
| CBLN2  |       |        |          |         |          |      |         |
| rs2217560 | PAH  | G      | 1.472 (0.937–2.313) | 0.693 | GG       | 4  (4.9%) | 32 (44.4%) | 41 (50.6%) | 7.742 (0.021) |
|        |       | A      |          |         | GA       | 10 (7.1%) | 37 (26.2%) | 94 (66.7%) |
|        | Non‑PAH |       |          |         | AA       |       |         |
| ALK1   |       |        |          |         |          |      |         |
| rs2277382 | PAH  | T      | 1.542 (0.762–3.121) | 0.228 | TT       | 1  (1.2%) | 13 (15.7%) | 69 (83.1%) | 2.551 (0.279) |
|        |       | C      |          |         | TC       | 0  (0.0%) | 19 (12.1%) | 138 (87.9%) |
|        | Non‑PAH |       |          |         | CC       |       |         |
| BMPR2  |       |        |          |         |          |      |         |
| rs34135567 | PAH  | D      | 3.815 (0.343–42.388) | 0.276 | D/CAA   | 2  (2.4%) | 80 (97.6%) | 1.381 (0.275) |
|        |       | CAA    |          |         | CAA/CAA |       |         |
| SMAD9  |       |        |          |         |          |      |         |
| rs141647648 | PAH  | D      | 0.813 (0.207–3.185) | 0.766 | D/AGATTA | 3  (3.6%) | 81 (96.4%) | 0.090 (0.529) |
|        | Non‑PAH |       |          |         | AGATTA/AGATTA |       |         |

All values were expressed as n (%). SNP: Single-nucleotide polymorphism; OR: Odds ratio; PAH: Pulmonary arterial hypertension.

Rs141647648 is a deletion/AGATTA in 3'-UTR of SMAD9. Allelic frequency and genotypic frequency in SLE-PAH and SLE-non-PAH group were 1.8% versus 2.2% (OR = 0.813, 95% CI = 0.207–3.185, P = 0.766) and 3.6% versus 4.4% (χ² = 0.09, P = 0.529), respectively.

This study attempted to explore the genetic susceptibility of PAH development in SLE. CBLN2 rs2217560 G allele was associated with an increased risk of 1.97 in a GWAS for iPAH and IPAH, which is in consistent with our result (OR = 1.951, 95% CI = 1.116–3.412, P = 0.019). CBLN2 gene encodes neuronal glycoprotein, which mainly expresses in the brain; it is also expressed in the lung, particularly in pulmonary vascular endothelial cells. CBLN2 peptide acts on vascular smooth muscle cell proliferation in a paracrine fashion and participates in pulmonary hypertension. We do not yet know the role of CBLN2 in lupus patients who developed PAH, but our results suggested that different etiologies lead to PAH in the same mechanism and CBLN2 might be a component of the common pathway.

Even though TGF-β signaling pathway has been proved to play an important role in iPAH and iPAH onset, previous studies on SSC-PAH did not report an association. The research on the Asian SLE-PAH population has regional characteristics; nevertheless, we could not find correlation of selected SNPs with PAH onset either. Considering that SSC and SLE both belong to the CTD spectrum, it is likely that PAH onset in CTD patients is distinct from iPAH patients and might have other genetic polymorphisms.

However, the sample number of SLE-PAH patients is still a limitation for the research to be more conclusive. According to the Genetic Power Calculator, over 560 samples were needed statistically. Further study with large database would be needed in order to obtain more genetic information on SLE-PAH patients.

In conclusion, the SNP discovered in GWAS in iPAH and PAH was proved to be associated with SLE-PAH, which revealed an important role of CBLN2 in PAH onset despite different etiologies. So far, we have not identified a correlation between the eight tested SNPs in TGF-β pathway and SLE-PAH onset. Further studies would be needed to reveal mechanism of PAH onset, and hopefully, more genetic study could provide a possibility for CTD-PAH early diagnosis and treatment.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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