Livedoid vasculopathy and its association with genetic variants: A systematic review

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Abstract
Livedoid vasculopathy (LV) is considered a disease of hypercoagulability. Association of LV with genetic variants is poorly characterised and large-scale genetic association studies have not been performed. The aim of the study was to systematically review variants in LV patients and to analyse the available clinical data. A systematic search of the literature in PubMed and Embase databases was performed to identify articles investigating genetic variation in LV patients. Thirty studies or case reports were identified that reported 265 LV patients tested for at least one out of six genetic variations. Among them, PAI-1 -675 4G/5G was the most common, accounting for 85.26% (81/95). Heterozygous 4G/5G was the major genotype. PAI-1 A844G, MTHFR C677T, and MTHFR A1298C were the second, third, and fourth most common variants in LV patients. Prothrombin G20210A and Factor V G1691A were mainly present in LV patients from Europe, North America, and South America. This review highlights the associations between LV and genetic variants. The distribution of variants may be geographically or ethnicity dependent; however, large sample case-control studies are needed to clarify associations.

KEYWORDS
genotype, plasminogen activator inhibitor-1, single-nucleotide polymorphism, variants, vascular disease

1 | INTRODUCTION

Livedoid vasculopathy (LV) was first described by Milian in 1929 and was also named atrophie blanche, segmental hyalinising vasculitis, and livedo reticularis with summer ulcerations.1 LV mainly affects young and middle-aged women with an incidence of 1:1000002 and presents with erythema, macules, painful ulcers, white satellite scars on both lower extremities. Hypercoagulability and thromboembolism in dermal vessels are the major causes of its pathogenesis. Therefore, the term LV is now frequently used to distinguish thrombo-occlusive vasculopathy from traditional cutaneous small vessel vasculitis.

A variety of hereditary and acquired coagulation abnormalities have been detected in LV patients, including polymorphisms in Methylene tetrahydrofolate reductase (MTHFR), Plasminogen activator inhibitor-1 (PAI-1), Prothrombin, and Factor V.3 The variants, including single-nucleotide polymorphisms, in the coagulation-related genes mentioned earlier can change or influence their expression and increase the risk of thrombosis, which contributes...
to the onset of LV. Furthermore, several case reports, case series, and other studies indicate the relationship between LV and certain genetic variants. However, no large-scale analyses have been conducted concerning genetic variants in LV. Here, we carried out a systematic review of the published literature, focusing on the polymorphisms C677T and A1298C in MTHFR, -675 4G/5G and A844G in PAI-1, G20210A in Prothrombin and G1691A in Factor V (the Leiden mutation), which have been reported in LV patients.

2 | METHODS

2.1 | Literature search

We screened PubMed and Embase databases on 14 September 2020 for articles concerning LV patients and genetic mutations (Figure 1). LV has a diversity of historic names and associated genes; therefore, the following broad search terms were applied: “livedoid vasculopathy”, “livedoid vasculitis”, “livedo vasculitis”, “atrophie blanche”, “white atrophy”, “segmental hyalinizing vasculitis”, “mutation”, “polymorphism”, “genotype”, “methylenetetrahydrofolate reductase”, “MTHFR”, “Plasminogen activator inhibitor-1”, “PAI-1”, “Prothrombin”, “Factor V”, and “Leiden”. Only studies, case series, and case reports published in English from inception of the databases to September 2020 were included. No other filters or restrictions were applied to the search.

![PRISMA flow figure of the literature review](image-url)

Key Messages
- Livedoid vasculopathy (LV) is considered a disease of hypercoagulability and its association with genetic variants is poorly characterised.
- In this systematic review, PAI-1 -675 4G/5G was the most common variant, PAI-1 A844G, MTHFR C677T, and MTHFR A1298C were the second, third, and fourth most common variants in LV patients, respectively.
- Prothrombin G20210A and Factor V G1691A were mainly present in LV patients from Europe, North America, and South America.
- This review highlights the associations between LV and genetic variants, the distribution of whom may be geographically or ethnicity dependent.

2.2 | Eligibility criteria

Inclusion criteria are as follows: (a) clinically and histologically confirmed LV diagnosis. Patients clinically presented as recurrent livedo reticularis, erythema, macules, painful ulcers, and white satellite scars on both lower extremities with intraluminal thrombosis, endothelial proliferation, and segmental hyalinisation in dermal vessels on histology. (b) At least one of the following variants were tested: MTHFR C677T and A1298C, PAI-1-675.
| No. | Authors                  | Year (year) | Patients (M/F) | Mean Age (year) | Country   | MTHFR C677T | MTHFR A1298C | PAI-1 -675 4G/5G | PAI-1 A844G | Prothrombin G20210A | Factor V G1691A |
|-----|--------------------------|-------------|----------------|-----------------|-----------|-------------|--------------|------------------|--------------|---------------------|-----------------|
| 1   | Tsai et al²              | 2009        | 56 (18/38)     | 29.79           | China     | 13/56       | 14/56        | 5/56             | 17/56        | 9/56                | NA              |
| 2   | Marsch et al³            | 2019        | 42 (15/27)     | NA              | Germany   | 10/25       | 8/25         | 7/25             | 14/25        | 12/17               | 7/17            |
| 3   | Lee et al⁴               | 2020        | 28 (8/20)      | 45.6            | Korea     | 4/24        | 13/24        | 7/24             | NA           | 17/17               | 7/17            |
| 4   | Agirbasli et al⁵         | 2011        | 20 (7/13)      | NA              | Turkey    | 5/20        | 4/20         | 11/20            | 4/20         | 15/16               | 1/16            |
| 5   | Hainstock et al⁶         | 2006        | 45 (15/32)     | NA              | America   | 5/14        | 6/14         | 3/14             | NA           | 1/1                 | 0/1             |
| 6   | Di Giacomo et al⁷        | 2010        | 34 (10/24)     | Brazil          | NA        | NS          | NS           | NS               | NS           | 28/34               | 6/34            |
| 7   | Da Costa Franca et al⁸   | 2009        | 14 (3/11)      | Brazil          | NA        | 5/14        | 6/14         | 3/14             | NA           | NA                  | NA              |
| 8   | Nakamura et al⁹          | 2011        | 3 (1/2)        | Japan           | NA        | 1/3         | 2/3          | 0/3              | NA           | NA                  | NA              |
| 9   | Yong et al¹⁰             | 2012        | 2 (0/2)        | Singapore       | NA        | 33.5        | NA           | NA               | 1/2          | NA                  | 2/2             |
| 10  | Biedermann et al¹¹        | 2000        | 1 (0/1)        | Germany         | NA        | 56          | NA           | NA               | NA           | 1/1                 | 1/1             |
| 11  | Mirra khimov et al¹²     | 2012        | 1 (0/1)        | America         | NA        | 87          | NA           | NA               | 1/1          | 1/1                 | 0/1             |
| 12  | Abou Rahal et al¹³        | 2012        | 1 (0/1)        | Lebanon         | NA        | 21          | 0/1          | 1/1              | 1/1          | 0/1                 | 0/1             |
| 13  | Irani-Hakime et al¹⁴     | 2008        | 1 (0/1)        | Lebanon         | NA        | 34          | 0/1          | 1/1              | 1/1          | 0/1                 | 1/1             |
| 14  | Deng et al¹⁵             | 2006        | 1 (0/1)        | America         | NA        | 33          | NA           | NA               | 1/1          | 0/1                 | 0/1             |
| 15  | Khenifer et al¹⁶         | 2009        | 1 (1/0)        | France          | NA        | 54          | NA           | NA               | 0/1          | 1/1                 | 1/1             |
| 16  | Calamia et al¹⁷          | 2002        | 1 (0/1)        | America         | NA        | 44          | NA           | NA               | 0/1          | 1/1                 | 1/1             |
| 17  | Kavala et al¹⁸           | 2008        | 1 (1/0)        | Turkey          | NA        | 19          | NA           | NA               | 0/1          | 1/1                 | 0/1             |
| 18  | Criado et al¹⁹           | 2013        | 1 (1/0)        | Brazil          | NA        | 13          | NA           | NA               | 0/1          | 1/1                 | 0/1             |
| 19  | Anavekar et al²⁰        | 2007        | 1 (0/1)        | Australia       | NA        | 53          | NA           | NA               | 0/1          | 1/1                 | 0/1             |
| 20  | Cardoso et al²¹          | 2007        | 1 (0/1)        | Portugal        | NA        | 31          | 0/1          | 1/1              | 0/1          | 1/1                 | 0/1             |
| 21  | Antunes et al²²          | 2010        | 1 (0/1)        | Portugal        | NA        | 25          | 0/1          | 1/1              | 0/1          | 1/1                 | 0/1             |
| 22  | Castillo-Martinez et al²³| 2014        | 1 (0/1)        | Mexico          | NA        | 12          | 0/1          | 1/1              | 0/1          | 1/1                 | 0/1             |
| 23  | Shankar et al²⁴          | 2013        | 1 (0/1)        | India           | NA        | 23          | 0/1          | 1/1              | 0/1          | 1/1                 | 0/1             |
| 24  | Davis et al²⁵            | 2008        | 1 (0/1)        | America         | NA        | 50          | NA           | NA               | 0/1          | 1/1                 | 0/1             |

(Continues)
4G/5G and A844G, Prothrombin G20210A and Factor V G1691A (the Leiden mutation). If patients were tested for several variants in an article, and heterozygosity or homozygosity were not clearly presented, then only the clearly recorded genotypes were enrolled. (c) Articles published in the English language. (d) Article types including case-control studies, case series, and case reports were enrolled.

Exclusion criteria are as follows: (a) the diagnosis of LV was uncertain; (b) heterozygosity or homozygosity of variants tested were not clearly recorded; (c) articles written in languages other than English; (d) review articles or editorial articles.

## RESULTS

After the extensive literature search, 53 articles were found in PubMed and Embase databases that concern genetic variants in LV patients. By carefully reviewing the full texts of these 53 articles, 30 were enrolled that complied with the inclusion and exclusion criteria (Table 1)\(^4\)\(^-\)\(^33\). A total of 265 patients, of whom 78 were male (29.43%) and 187 were female (70.57%) giving a female to male ratio of 2.4:1, were tested for at least one out of the following six genetic variants, \textit{MTHFR} C677T and A1298C, \textit{PAI-1} -675 4G/5G and A844G, and \textit{Prothrombin} G20210A and \textit{Factor V} G1691A. The mean patient age was 35.74 years (range: 12–87 years). Single nucleotide polymorphisms (SNPs) were assessed by polymerase chain reaction (PCR), \textit{Hind} III restriction fragment length polymorphism (RFLP), or sequencing. The ref SNP ID, location, and affected function are summarised in Table 2.

### 3.1 SNPs

#### 3.1.1 MTHFR C677T

Thirteen articles presented LV patients that were examined for \textit{MTHFR} C677T,\(^4\)\(^-\)\(^6\),\(^9\)\(^-\)\(^11\),\(^15\),\(^16\),\(^23\),\(^25\),\(^26\),\(^30\),\(^32\) although one article referred vaguely to its heterozygosity or homozygosity.\(^9\) A total of 129 patients were tested for \textit{MTHFR} C677T, of which 46 had the heterozygous CT genotype (35.66%) and 25 had the homozygous TT genotype (19.38%). Thus, the total carrier rate of \textit{MTHFR} C677T was 55.04% (71/129).

#### 3.1.2 MTHFR A1298C

There were only two studies and one case report concerning \textit{MTHFR} A1298C in LV patients.\(^3\),\(^5\),\(^31\) In all, 82 LV
patients were tested for MTHFR A1298C. Twenty-nine patients had the AC genotype (a heterozygous carrier rate of 35.67%) and seven had the CC genotype (a homozygous carrier rate of 8.54%). The carrier rate of MTHFR A1298C was 43.90% (36/82).

### 3.1.3 | PAI-1 -675 4G/5G

Three studies and two case reports presented assessment of PAI-1 -675 4G/5G in a total of 95 LV patients.²⁴ Twenty-eight of 95 LV patients (29.47%) displayed the homozygous 4G/4G genotype, whereas 53 of 95 LV patients (55.79%) showed the heterozygous 4G/5G genotype. The total carrier rate of PAI-1 -675 4G/5G was 85.26% (81/95), which was the highest carrier rate among the assessed SNPs.

### 3.1.4 | PAI-1 A844G

Compared to PAI-1 -675 4G/5G, the variant PAI-1 A844G has been rarely assessed in LV patients. Only two articles, including one study and one case report, have reported a total of 18 LV patients tested for PAI-1 A844G.³² Fifty percent of tested LV patients (9/18) had the heterozygous AG genotype, while only one tested LV patient (5.56%) was homozygous for the GG genotype. The carrier rate of PAI-1 A844G was 55.56% (10/18).

### 3.1.5 | Prothrombin G20210A

Eighty-five LV patients from 15 studies or case reports were evaluated for Prothrombin G20210A, while patients from another three studies were excluded because of vague descriptions of heterozygosity or homozygosity.⁸-¹⁰ The total carrier rate of Prothrombin G20210A was 10.59% (9/85), which was the lowest carrier rate of the six SNPs assessed. All the LV patients with Prothrombin G20210A displayed a heterozygous GA genotype (9/85); no homozygous AA carrier was identified (0/85).

### 3.1.6 | Factor V G1691A

The total carrier rate of Factor V G1691A (14.07%) in LV patients was the second lowest among the tested SNPs. From 23 articles,³¹ 135 LV patients were tested. In one study,¹⁰ heterozygosity or homozygosity was not clearly stated; however, the remaining studies showed 19 patients to have the heterozygous GA genotype and no patients to have the homozygous AA genotype (0/135).

### 3.2 | Regional distribution

Most articles did not refer in detail to the ethnicity or race of patients; therefore, we tried to determine the association between regions and genotypes in LV patients,
which may provide clues for relationships between ethnicity and genotypes in LV. Patients were identified from 17 countries and 5 continents involving Asia, Europe, North America, South America, and Oceania (Table 3). The heterozygous, homozygous, and total carrier rates of each SNP are summarised in Table 4.

### Table 3  Summary of region and general data of articles enrolled

| No. | Country        | Authors            | Year | Patients (M/F) | Mean age (year) |
|-----|----------------|--------------------|------|----------------|-----------------|
| 1   | China          | Tsai et al\(^4\)  | 2009 | 56 (18/38)     | 29.79           |
| 2   | Japan          | Nakamura et al\(^1\) | 2011 | 3 (1/2)        | 36              |
| 3   | Singapore      | Yong et al\(^1\)  | 2012 | 2 (0/2)        | 33.5            |
| 4   | Lebanon        | Abou Rahal et al\(^5\) | 2012 | 1 (0/1)       | 21               |
| 5   | Lebanon        | Irani-Hakime et al\(^6\) | 2008 | 1 (0/1)       | 34               |
| 6   | Turkey         | Kavala et al\(^7\) | 2008 | 1 (1/0)        | 19               |
| 7   | India          | Shankar et al\(^8\) | 2013 | 1 (0/1)       | 23               |
| 8   | Turkey         | Sahin et al\(^9\)  | 2017 | 1 (0/1)        | 15               |
| 9   | Korea          | Lee et al\(^10\)   | 2020 | 28 (8/20)      | 45.6            |
| 10  | Turkey         | Agirbasli et al\(^1\) | 2011 | 20 (7/13)     | 26               |
| 11  | Afghan         | Brockley et al\(^1\) | 2013 | 1 (1/0)       | 17               |
| 1   | America        | Hairston et al\(^1\) | 2006 | 45 (13/32)     | 45               |
| 2   | America        | Mirrakhimov et al\(^1\) | 2012 | 1 (0/1)       | 87               |
| 3   | America        | Deng et al\(^1\)  | 2006 | 1 (0/1)        | 33               |
| 4   | Mexico         | Castillo-Martínez et al\(^1\) | 2014 | 1 (0/1)     | 12               |
| 5   | America        | Davis et al\(^1\) | 2008 | 1 (0/1)        | 50               |
| 6   | America        | Gotlib et al\(^1\) | 2003 | 1 (0/1)        | 30               |
| 7   | America        | Calamia et al\(^1\) | 2002 | 1 (0/1)       | 44               |
| 1   | Portugal       | Cardoso et al\(^1\) | 2007 | 1 (0/1)       | 31               |
| 2   | Portugal       | Antunes et al\(^1\) | 2010 | 1 (0/1)       | 25               |
| 3   | Portugal       | Morais et al\(^1\) | 2010 | 1 (0/1)       | 19               |
| 4   | Spain          | Vázquez et al\(^1\) | 2018 | 1 (1/0)       | 64               |
| 5   | Britain        | Wong et al\(^1\)  | 2011 | 1 (0/1)       | 34               |
| 6   | Germany        | Biedermann et al\(^1\) | 2000 | 1 (0/1)      | 56               |
| 7   | France         | Khenifer et al\(^1\) | 2009 | 1 (1/0)       | 54               |
| 8   | Germany        | Marsch et al\(^1\) | 2019 | 42 (15/27)     | NA               |
| 1   | Brazil         | Di Giacomo et al\(^1\) | 2010 | 34 (10/24)    | 45               |
| 2   | Brazil         | Da Costa Franca et al\(^1\) | 2009 | 14 (1/13)    | 41.5             |
| 3   | Brazil         | Criado et al\(^1\) | 2013 | 1 (1/0)       | 13               |
| 1   | Australia      | Anavekar et al\(^1\) | 2007 | 1 (0/1)       | 53               |

Abbreviations: F, female; M, male; NA, not available.

### 3.2.1  Asia

In Asia, there were 11 studies or case reports from eight countries including China,\(^4\) Japan,\(^11\) Singapore,\(^12\) Lebanon,\(^15,16\) Turkey,\(^7,20,31\) India,\(^26\) South Korea,\(^6\) and Afghanistan.\(^29\) A total of 115 LV patients, of whom 36 were male...
### TABLE 4  Genotypes polymorphisms results in LV patients from five continents

| Continents     | Patients (M/F) | Mean age (year) | Countries | Articles | MTHFR C677T | MTHFR A1298C | PAI-1 -675 4G/5G |
|----------------|----------------|-----------------|-----------|----------|-------------|--------------|-----------------|
|                |                |                 |           |          | Heterozygous | Homozygous   | Heterozygous    |
|                |                |                 |           |          | Total       | Heterozygous | Total           |
|                |                |                 |           |          | Homozygous  | Total       | Homozygous      |
|                |                |                 |           |          | Total       | Homozygous  | Total           |
| Asia           | 115 (36/79)    | 27.26           | 8         | 11       | 34.88%      | 16.27%       | 51.15%          |
|                |                |                 |           |          | 36.84%      | 7.02%        | 43.86%          |
|                |                |                 |           |          | 53.95%      | 28.95%       | 82.90%          |
| Europe         | 49 (17/32)     | 40.43           | 5         | 8        | 32.14%      | 32.14%       | 64.28%          |
|                |                |                 |           |          | 32%         | 12%          | 44%             |
|                |                |                 |           |          | 66.67%      | 27.78%       | 94.45%          |
| North America  | 51 (13/38)     | 43              | 2         | 7        | 0%          | 0%           | NA              |
|                |                |                 |           |          | NA          | NA           | NA              |
| South America  | 49 (12/37)     | 33.17           | 1         | 3        | 42.86%      | 21.43%       | 64.29%          |
|                |                |                 |           |          | NA          | NA           | NA              |
| Oceania        | 1 (0/1)        | 53              | 1         | 1        | NA          | NA           | NA              |
|                |                |                 |           |          | NA          | NA           | NA              |
| Total          | 265 (78/187)   | 35.74           | 17        | 30       | 35.66%      | 19.38%       | 50.04%          |
|                |                |                 |           |          | 35.67%      | 8.54%        | 43.90%          |
|                |                |                 |           |          | 55.79%      | 29.47%       | 85.26%          |

| Continents     | Patients (M/F) | Mean age (year) | Countries | Articles | PAI-1 A844G | Prothrombin G20210A | Factor V G1691A |
|----------------|----------------|-----------------|-----------|----------|-------------|---------------------|----------------|
|                |                |                 |           |          | Heterozygous | Homozygous          | Heterozygous    |
|                |                |                 |           |          | Total       | Homozygous          | Total           |
|                |                |                 |           |          | Homozygous  | Total               | Homozygous      |
|                |                |                 |           |          | Total       | Homozygous          | Total           |
| Asia           | 115 (36/79)    | 27.26           | 8         | 11       | NA          | NA                  | NA              |
|                |                |                 |           |          | 1.67%       | 0%                  | 1.67%           |
|                |                |                 |           |          | 6.45%       | 0%                  | 6.45%           |
| Europe         | 49 (17/32)     | 40.43           | 5         | 8        | 50%         | 5.56%               | 55.56%          |
|                |                |                 |           |          | 15.79%      | 0%                  | 21.74%          |
|                |                |                 |           |          | 21.74%      | 0%                  | 21.74%          |
| North America  | 51 (13/38)     | 43              | 2         | 7        | NA          | NA                  | NA              |
|                |                |                 |           |          | 75%         | 0%                  | 75%             |
|                |                |                 |           |          | 28.57%      | 0%                  | 28.57%          |
| South America  | 49 (12/37)     | 33.17           | 1         | 3        | NA          | NA                  | NA              |
|                |                |                 |           |          | 100%        | 0%                  | 100%            |
|                |                |                 |           |          | 17.14%      | 0%                  | 17.14%          |
| Oceania        | 1 (0/1)        | 53              | 1         | 1        | NA          | NA                  | NA              |
|                |                |                 |           |          | 100%        | 0%                  | 100%            |
|                |                |                 |           |          | 0%          | 0%                  | 0%              |
| Total          | 265 (78/187)   | 35.74           | 17        | 30       | 50%         | 5.56%               | 55.56%          |
|                |                |                 |           |          | 10.59%      | 0%                  | 14.07%          |

Abbreviations: F, female; M, male; and NA, not available.
(31.30%) and 79 were female (68.70%), with a mean age of 27.26 years were evaluated. The variant carriers were for 51.15% for \textit{MTHFR} C677T, 43.86% for \textit{MTHFR} A1298C, 82.9% for \textit{PAI-1} -675 4G/5G, 1.67% for \textit{Prothrombin} G20210A, and 6.45% in \textit{Factor V} G1691A. The \textit{PAI-1} A844G polymorphism has not yet been tested in Asian populations.

3.2.2 | Europe

In Europe, there were eight articles involving 49 LV patients from five countries, including Portugal,\textsuperscript{23,24,30} Spain,\textsuperscript{32} Britain,\textsuperscript{33} Germany,\textsuperscript{5,13} and France.\textsuperscript{18} The female to male ratio was 1.88:1, and the mean age of these LV patients was 40.43 years. The variant carrier rates were 64.28% for \textit{MTHFR} C677T, 44% for \textit{MTHFR} A1298C, 94.45% for \textit{PAI-1} -675 4G/5G, 55.56% for \textit{PAI-1} A844G, 15.79% for \textit{Prothrombin} G20210A, and 21.74% for \textit{Factor V} G1691A.

3.2.3 | North America

In North America, seven studies or case reports were enrolled; one article was partially excluded because of a lack of description of heterozygosities or homozygosities.\textsuperscript{8} Six out of the seven articles were conducted in America,\textsuperscript{8,14,17,19,27,28} the other was from Mexico.\textsuperscript{25} A total of 51 LV patients from North America, 13 males and 38 females with a mean age of 43 years, were tested for genetic variation. The total mutation carrier rates were 75% for \textit{Prothrombin} G20210A and 28.57% for \textit{Factor V} G1691A. There were only case reports for carriers of wild-type \textit{MTHFR} C677T and \textit{PAI-1} -675 4G/5G. \textit{MTHFR} A1298C and \textit{PAI-1} A844G have not yet been tested in North America.

3.2.4 | South America

There were three studies conducted in South America, all in Brazil,\textsuperscript{9,10,22} and two of them only vaguely described mutations in \textit{MTHFR}, \textit{Prothrombin} G20210A, and \textit{Factor V} G1691A, was and so were partially ignored.\textsuperscript{9,10} There were a total of 49 LV patients consisting of 12 males and 37 females, with a mean age of 33.17 years. The carrier rate of \textit{MTHFR} C677T and \textit{Factor V} G1691A was 64.29% and 17.14%, respectively.

3.2.5 | Oceania

In Oceania, only one case report from Australia was identified. A 53-year-old female LV patient was tested for \textit{Prothrombin} G20210A and \textit{Factor V} G1691A and showed a heterozygous GA genotype for \textit{Prothrombin} G20210A.\textsuperscript{22}

4 | DISCUSSION

LV mainly affects female patients with a female to male ratio of 2.4:1. The mean age ranges from 27.26 to 53 years in the five continents, with an earlier disease onset in Asian populations compared to LV patients in Europe, South America, and North America. Feng et al emphasised that the peak age at disease onset was much younger in Chinese LV patients than that in the published literature.\textsuperscript{40} Our review findings of the demographic data are consistent with the results of Feng et al and also provide the clinical characteristics of early onset in Asian LV patients.

Currently, hypercoagulability and abnormalities in coagulation function are considered the main mechanisms of pathogenesis in LV. Platelets, coagulation and anti-coagulation system, and fibrinolysis system maintain dynamic balance and participate in physiological haemostasis and removal of abnormal blood clots. The six variants examined in this review are known to participate in the development of hypercoagulability and thrombophilia by acting on different pathways. \textit{MTHFR} C677T and A1298C promote the prethrombotic state by affecting homocysteine levels through folate metabolism,\textsuperscript{41} the metabolites of which cause damage to vascular endothelial cells, whereas \textit{PAI-1} -675 4G/5G and A844G, \textit{Prothrombin} G20210A and \textit{Factor V} G1691A influence the endogenous fibrinolytic system and coagulation function, increasing the risk of hypercoagulability. In this review, we found that \textit{PAI-1} -675 4G/5G was the most common variant in LV patients, accounting for 85.26%. \textit{PAI-1} A844G, \textit{MTHFR} C677T, and \textit{MTHFR} A1298C were the second, third, and fourth most commonly existing variants in LV patients. The carrier rates of \textit{Prothrombin} G20210A and \textit{Factor V} G1691A were at relatively lower percentages.

The epidemiology of these variants may vary depending on geography and ethnicity. Grouped by continents, LV patients from Asia and Europe demonstrated higher rates of \textit{PAI-1} -675 4G/5G, with heterozygous 4G/5G being the major genotype that accounted for over 50% of variants. Although the total carrier rate of \textit{PAI-1} A844G was more than 50% in European LV patients, up to now \textit{PAI-1} A844G has only been detected in LV patients from Europe. \textit{PAI-1} A844G has not been detected in LV patients from continents other than Europe. The carrier rate of \textit{MTHFR} C677T was slightly higher in LV patients from Europe and South America. However, there was no significant difference in the \textit{MTHFR} A1298C rate between LV patients in Asia and
Europe. Prothrombin G20210A and Factor V G1691A showed relatively lower carrier rates; however, compared with LV patients from Asia, rates in LV patients from Europe, North America and South America were higher.

In this review, PAI-1 -675 4G/5G was the most frequently detected variant and by influencing the expression of PAI-1 it is involved in the pathogenesis of LV. The 4G allele results in a higher PAI-1 expression level.\(^6\) Even though overexpression and enhanced activity of PAI-1 have been detected in LV patients, its role in pathogenesis remains unclear.\(^7,42\) PAI-1 is probably involved in far more processes than just thrombosis; it may play roles in other pathophysiological processes and activities, such as cell adhesion, migration, and angiogenesis.\(^43\) Tissue-type plasminogen activator (tPA) treatment targeting PAI-1 is regarded as a promising therapy for LV.\(^44\) The tPA therapy was reported to be effective in LV patients with PAI-1 -675 4G/4G homozygous genotype.\(^17,24\) Therefore, PAI-1 in LV pathogenesis warrants further study.

This review has explored the association between LV and genetic variation. However, few case control studies were enrolled, with case series and case reports being the main resource. Ideally, a large scale case-control study of genetic variation in LV patients should be performed. And the multilocus effects by multifactor dimensionality reduction indicating gene-gene interaction and gene-environmental interactions may probably provide new insight into LV in further case-control study.

5 | CONCLUSIONS

In this review of six variants in LV patients, PAI-1 -675 4G/5G was the most common and accounted for 85.26% (81/95) with heterozygous 4G/5G the major genotype; PAI-1 A844G, MTHFR C677T, and MTHFR A1298C were the second, third, and fourth most common variants in LV patients. Because the cause of LV is still unknown and no large sample case-control study has been performed, our review of LV and its association with genetic variants may facilitate further basic research and clinical treatment. In particular, our regional analysis may enable further research to be targeted according to geography and ethnicity.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable - no new data generated

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