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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 1:100000[2] 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 *Methylenetetrahydrofolate 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 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.

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 | 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.

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

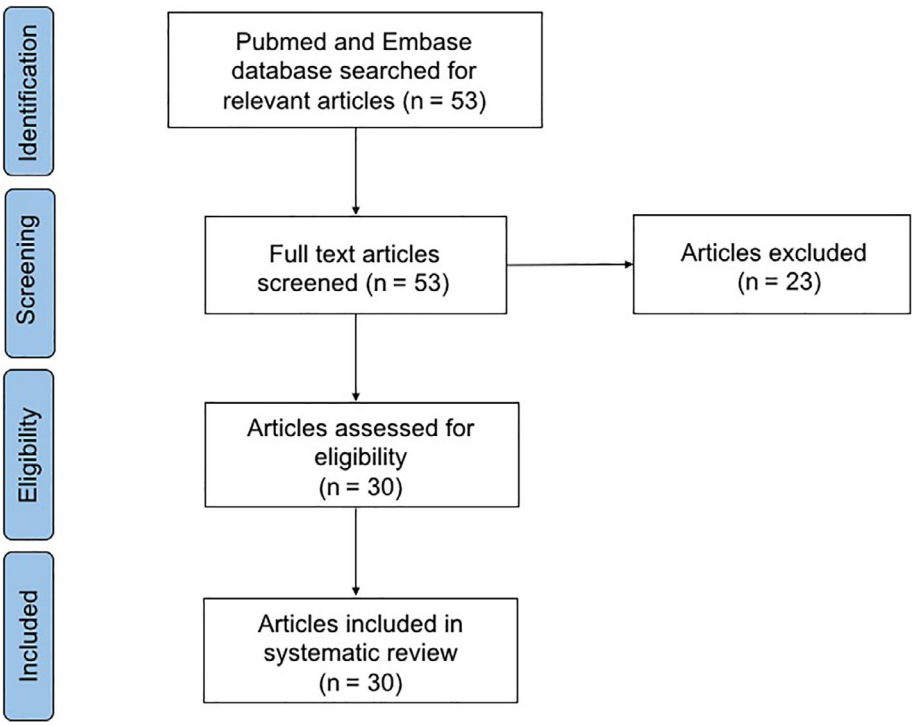

FIGURE 1 PRISMA flow figure of the literature review

TABLE 1 LV patients tested for *MTHFR* C677T, *MTHFR* A1298C, *PAI-1* -675 4G/5G, *PAI-1* A844G, *prothrombin* G20210A, and *Factor V* G1691A genotype polymorphisms

						MTHFR C677T			MTHFR A1298C			PAI-1 -675 4G/5G			PAI-1 A844G			Prothrombin G20210A			Factor V G1691A		
No.	Authors	Year	Patients (M/F)	Mean Age (year)	Country	CC	CT	TT	AA	AC	CC	4G/4G	4G/5G	5G/5G	AA	AG	GG	GG	GA	AA	GG	GA	AA
1	Tsai et al[4]	2009	56 (18/38)	29.79	China	37/56	14/56	5/56	32/56	20/56	4/56	17/56	30/56	9/56	NA	NA	NA	56/56	0/56	0/56	56/56	0/56	0/56
2	Marsch et al[5]	2019	42 (15/27)	NA	Germany	10/25	8/25	7/25	14/25	8/25	3/25	4/17	12/17	1/17	7/17	9/17	1/17	15/16	1/16	0/16	14/17	3/17	0/17
3	Lee et al[6]	2020	28 (8/20)	45.6	Korea	4/24	13/24	7/24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4	Agirbasli et al[7]	2011	20 (7/13)	26	Turkey	NA	NA	NA	NA	NA	NA	5/20	11/20	4/20	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	Hairston et al[8]	2006	45 (13/32)	45	America	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NS	NS	NS	7/9	2/9	0/9
6	Di Giacomo et al[9]	2010	34 (10/24)	45	Brazil	NS	NS	NS	NS	NS	NS	NA	NA	NA	NA	NA	NA	NS	NS	NS	28/34	6/34	0/34
7	Da Costa Franca et al[10]	2009	14 (1/13)	41.5	Brazil	5/14	6/14	3/14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NS	NS	NS	NS	NS	NS
8	Nakamura et al[11]	2011	3 (1/2)	36	Japan	1/3	2/3	0/3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	Yong et al[12]	2012	2 (0/2)	33.5	Singapore	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/2	2/2	0/2
10	Biedermann et al[13]	2000	1 (0/1)	56	Germany	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1
11	Mirrakhimov et al[14]	2012	1 (0/1)	87	America	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	1/1	0/1	0/1
12	Abou Rahal et al[15]	2012	1 (0/1)	21	Lebanon	0/1	0/1	1/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	1/1	0/1	0/1
13	Irani-Hakime et al[16]	2008	1 (0/1)	34	Lebanon	0/1	0/1	1/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	0/1	1/1	0/1
14	Deng et al[17]	2006	1 (0/1)	33	America	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1
15	Khenifer et al[18]	2009	1 (1/0)	54	France	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	0/1	1/1	0/1
16	Calamia et al[19]	2002	1 (0/1)	44	America	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1
17	Kavala et al[20]	2008	1 (1/0)	19	Turkey	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1
18	Criado et al[21]	2013	1 (1/0)	13	Brazil	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	1/1	0/1	0/1
19	Anavekar et al[22]	2007	1 (0/1)	53	Australia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	1/1	0/1	0/1
20	Cardoso et al[23]	2007	1 (0/1)	31	Portugal	0/1	0/1	1/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	1/1	0/1	0/1
21	Antunes et al[24]	2010	1 (0/1)	25	Portugal	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	NA	NA	NA	0/1	1/1	0/1	1/1	0/1	0/1
22	Castillo-Martínez et al[25]	2014	1 (0/1)	12	Mexico	1/1	0/1	0/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	1/1	0/1	0/1
23	Shankar et al[26]	2013	1 (0/1)	23	India	0/1	1/1	0/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
24	Davis et al[27]	2008	1 (0/1)	50	America	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	0/1	1/1	0/1

TABLE 1 (Continued)

No.	Authors	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		
						CC	CT	TT	AA	AC	CC	4G/4G	4G/5G	5G/5G	AA	AG	GG	GG	GA	AA	GG	GA	AA
25	Gotlib et al[28]	2003	1 (0/1)	30	America	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/1	1/1	0/1	NA	NA	NA
26	Brockley et al[29]	2013	1 (1/0)	17	Afghan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	NA	NA	NA
27	Morais et al[30]	2010	1 (0/1)	19	Portugal	0/1	1/1	0/1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
28	Sahin et al[31]	2017	1 (0/1)	15	Turkey	NA	NA	NA	0/1	1/1	0/1	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	1/1	0/1	0/1
29	Vázquez et al[32]	2018	1 (1/0)	64	Spain	0/1	0/1	1/1	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1	NA	NA	NA	1/1	0/1	0/1
30	Wong et al[33]	2011	1 (0/1)	34	Britain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1/1	0/1	0/1

Abbreviations: F, female; LV, livedoid vasculopathy; NA, not available; NS, not stated (heterozygosity or homozygosity of mutations not stated clearly); M, male.

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.

3 | 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, *MTHFR* C677T and A1298C, *PAI-1* -675 4G/5G and A844G, and *Prothrombin* G20210A and *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), *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 *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 *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 *MTHFR* C677T was 55.04% (71/129).

3.1.2 | *MTHFR* A1298C

There were only two studies and one case report concerning *MTHFR* A1298C in LV patients.[4,5,31] In all, 82 LV

TABLE 2 Summary of background information about SNPs discussed in LV

Genotypes	Ref SNP ID	Location	Chromosome	Mutation	Alter in function
MTHFR C677T	rs1801133	Nucleotide 677 of exon 4	1p36.3	C>T	To reduce 60% in MTHFR enzyme activity and to rise 20% in homocysteine levels[34]
MTHFR A1298C	rs1801131	Nucleotide 1298 of exon 7	1p36.3	A>C	A mild form of MTHFR deficiency with hyperhomocysteinemia[35]
PAI-1 -675 4G/5G	rs1799889	Promoter-675 region	7q21.3-q22	G deletion or insertion	PAI-1 levels in the 4G/4G genotype were approximately 25% higher than those in the 5G/5G genotype[36]
PAI-1 A844G	rs2227631	Promoter-844 region	7q21.3-q22	A>G	Together with *PAI-1* -675 4G/5G to affect transcriptional activity of the *PAI-1* gene[37]
Prothrombin G20210A	rs1799963	Position 20 210 in the 3′-untranslated region	11p11-q12	G>A	Increased level of prothrombin mRNA and protein with a more effective poly(A) site[38]
Factor V G1691A	rs6025	Nucleotide 1691 of exon 10	1q23	G>A	Poor anticoagulant response to activated Protein C that inactivates Factors Va and VIIIa[39]

Abbreviations: A, adenine; C, cytosine; G, guanine; LV, livedoid vasculopathy; and T, thymine.

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.[4,5,7,17,24] 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.[5,32] 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,[4,5,14-16,18,21-25,27-29,31] 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,[4,5,8-10,12-25,27,31-33] 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,

TABLE 3 Summary of region and general data of articles enrolled

No.	Country	Authors	Year	Patients (M/F)	Mean age (year)
	Asia				
1	China	Tsai et al[4]	2009	56 (18/38)	29.79
2	Japan	Nakamura et al[11]	2011	3 (1/2)	36
3	Singapore	Yong et al[12]	2012	2 (0/2)	33.5
4	Lebanon	Abou Rahal et al[15]	2012	1 (0/1)	21
5	Lebanon	Irani-Hakime et al[16]	2008	1 (0/1)	34
6	Turkey	Kavala et al[20]	2008	1 (1/0)	19
7	India	Shankar et al[26]	2013	1 (0/1)	23
8	Turkey	Sahin et al[31]	2017	1 (0/1)	15
9	Korea	Lee et al[6]	2020	28 (8/20)	45.6
10	Turkey	Agirbasli et al[7]	2011	20 (7/13)	26
11	Afghan	Brockley et al[29]	2013	1 (1/0)	17
	North America				
1	America	Hairston et al[8]	2006	45 (13/32)	45
2	America	Mirrakhimov et al[14]	2012	1 (0/1)	87
3	America	Deng et al[17]	2006	1 (0/1)	33
4	Mexico	Castillo-Martínez et al[25]	2014	1 (0/1)	12
5	America	Davis et al[27]	2008	1 (0/1)	50
6	America	Gotlib et al[28]	2003	1 (0/1)	30
7	America	Calamia et al[19]	2002	1 (0/1)	44
	Europe				
1	Portugal	Cardoso et al[23]	2007	1 (0/1)	31
2	Portugal	Antunes et al[24]	2010	1 (0/1)	25
3	Portugal	Morais et al[30]	2010	1 (0/1)	19
4	Spain	Vázquez et al[32]	2018	1 (1/0)	64
5	Britain	Wong et al[33]	2011	1 (0/1)	34
6	Germany	Biedermann et al[13]	2000	1 (0/1)	56
7	France	Khenifer et al[18]	2009	1 (1/0)	54
8	Germany	Marsch et al[5]	2019	42 (15/27)	NA
	South America				
1	Brazil	Di Giacomo et al[9]	2010	34 (10/24)	45
2	Brazil	Da Costa Franca et al[10]	2009	14 (1/13)	41.5
3	Brazil	Criado et al[21]	2013	1 (1/0)	13
	Oceania				
1	Australia	Anavekar et al[22]	2007	1 (0/1)	53

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

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.

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 Heterozygous	Homozygous	Total	MTHFR A1298C Heterozygous	Homozygous	Total	PAI-1 -675 4G/5G Heterozygous	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%	0%	NA	NA	NA	0%	0%	0%
South America	49 (12/37)	33.17	1	3	42.86%	21.43%	64.29%	NA	NA	NA	NA	NA	NA
Oceania	1 (0/1)	53	1	1	NA	NA	NA	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 Heterozygous	Homozygous	Total	Prothrombin G20210A Heterozygous	Homozygous	Total	Factor V G1691A Heterozygous	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%	15.79%	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%	10.59%	14.07%	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 *MTHFR* C677T, 43.86% for *MTHFR* A1298C, 82.9% for *PAI-1* -675 4G/5G, 1.67% for *Prothrombin* G20210A, and 6.45% in *Factor V* G1691A. The *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,[23,24,30] Spain,[32] Britain,[33] Germany,[5,13] and France.[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 *MTHFR* C677T, 44% for *MTHFR* A1298C, 94.45% for *PAI-1* -675 4G/5G, 55.56% for *PAI-1* A844G, 15.79% for *Prothrombin* G20210A, and 21.74% for *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 heterozygosity or homozygosity.[8] Six out of the seven articles were conducted in America,[8,14,17,19,27,28] the other was from Mexico.[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 *Prothrombin* G20210A and 28.57% for *Factor V* G1691A. There were only case reports for carriers of wild-type *MTHFR* C677T and *PAI-1* -675 4G/5G. *MTHFR* A1298C and *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,[9,10,21] and two of them only vaguely described mutations in *MTHFR*, *Prothrombin* G20210A, and *Factor V* G1691A, was and so were partially ignored.[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 *MTHFR* C677T and *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 *Prothrombin* G20210A and *Factor V* G1691A and showed a heterozygous GA genotype for *Prothrombin* G20210A.[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.[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 anticoagulation 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. *MTHFR* C677T and A1298C promote the prethrombotic state by affecting homocysteine levels through folate metabolism,[41] the metabolites of which cause damage to vascular endothelial cells, whereas *PAI-1* -675 4G/5G and A844G, *Prothrombin* G20210A and *Factor V* G1691A influence the endogenous fibrinolytic system and coagulation function, increasing the risk of hypercoagulability. In this review, we found that *PAI-1* -675 4G/5G was the most common variant in LV patients, accounting for 85.26%. *PAI-1* A844G, *MTHFR* C677T, and *MTHFR* A1298C were the second, third, and fourth most commonly existing variants in LV patients. The carrier rates of *Prothrombin* G20210A and *Factor V* G1691A were at relatively lower percentages.

The epidemiology of theses variants may vary depending on geography and ethnicity. Grouped by continents, LV patients from Asia and Europe demonstrated higher rates of *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 *PAI-1* A844G was more than 50% in European LV patients, up to now *PAI-1* A844G has only been detected in LV patients from Europe. *PAI-1* A844G has not been detected in LV patients from continents other than Europe. The carrier rate of *MTHFR* C677T was slightly higher in LV patients from Europe and South America. However, there was no significant difference in the *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.[36] 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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REFERENCES

1. Feldaker M, Hines EA Jr, Kierland RR. Livedo reticularis with summer ulcerations. *AMA Arch Derm*. 1955;72(1):31-42.
2. Pulido-Pérez A, Avilés-Izquierdo JA, Suárez-Fernández R. Cutaneous vasculitis. *Actas Dermosifiliogr*. 2012;103(3):179-191.
3. Kerk N, Goerge T. Livedoid vasculopathy—current aspects of diagnosis and treatment of cutaneous infarction. *J German Soc Dermatol*. 2013;11(5):407-410.
4. Tsai TF, Yang CH, Chu CY, Liou YH, Hsiao WC, Lin CT, Wu LS. Polymorphisms of MTHFR gene associated with livedoid vasculopathy in Taiwanese population. *J Dermatol Sci*. 2009;54(3):214-216.
5. Marsch WC, Komatsuzaki S, Mueller A, Hagemann M, Lange D, Maemecke L, Villavicencio-Lorini P, Hoffmann K. Livedoid vasculopathy: does hyperhomocysteinaemia play an aetiological role?. *Eur J Dermatol*. 2019;29(3):287-293.
6. Lee JS, Cho S. Methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism in Korean livedoid vasculopathy patients. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2020.05.158.
7. Agirbasli M, Eren M, Eren F, Murphy SB, Serdar ZA, Seckin D, Zara T, Cem Mat M, Demirkesen C, Vaughan DE. Enhanced functional stability of plasminogen activator inhibitor-1 in patients with livedoid vasculopathy. *J Thromb Thrombolysis*. 2011;32(1):59-63.
8. Hairston BR, Davis MD, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. *Arch Dermatol*. 2006;142(11):1413-1418.
9. Di Giacomo TB, Hussein TP, Souza DG, Criado PR. Frequency of thrombophilia determinant factors in patients with livedoid vasculopathy and treatment with anticoagulant drugs—a prospective study. *J Eur Acad Dermatol Venereol*. 2010;24(11):1340-1346.
10. Da Costa Franca AFE, De Moraes Mazetto B, Orsi FA, De Paula EV, Machado TFGS, Souza EM, Annichino-Bizzacchi JM. Adamts13 activity and von willebrand factor levels in patients with livedoid vasculopathy. *Blood*. 2009;114:22.
11. Nakamura S, Kishibe M, Nishi K, Hashimoto Y, Takeda K, Mizumoto T, Iizuka H. Livedoid vasculopathy; favorable clinical response with low dose warfarin. *Eur J Dermatol*. 2011;21(6):1011-1012.
12. Yong AA, Tan AW, Giam YC, Tang MB. Livedoid vasculopathy and its association with factor V Leiden mutation. *Singapore Med J*. 2012;53(12):e258-e260.
13. Biedermann T, Flaig MJ, Sander CA. Livedoid vasculopathy in a patient with factor V mutation (Leiden). *J Cutan Pathol*. 2000;27(8):410-412.
14. Mirrakhimov AE, Velasquez Kho E, Ali A. Painless Livedoid vasculopathy in a patient with G20210A Prothrombin gene mutation. *Case Rep Med*. 2012;2012:910231.
15. Abou Rahal J, Ishak RS, Otrock ZK, Kibbi AG, Taher AT. Livedoid vasculopathy in a patient with lupus anticoagulant and MTHFR mutation: treatment with low-molecular-weight heparin. *J Thromb Thrombolysis*. 2012;34(4):541-544.
16. Irani-Hakime NA, Stephan F, Kreidy R, Jureidini I, Almawi WY. Livedoid vasculopathy associated with combined prothrombin G20210A and factor V (Leiden) heterozygosity and MTHFR C677T homozygosity. *J Thromb Thrombolysis*. 2008;26(1):31-34.

17. Deng A, Gocke CD, Hess J, Heyman M, Paltiel M, Gaspari A. Livedoid vasculopathy associated with plasminogen activator inhibitor-1 promoter homozygosity (4G/4G) treated successfully with tissue plasminogen activator. *Arch Dermatol*. 2006; 142(11):1466-1469.
18. Khenifer S, Thomas L, Balme B, Dalle S. Livedoid vasculiltis associated with a double heterozygous Factor V Leiden and prothrombin G20210A gene mutations. *Clin Exp Dermatol*. 2009;34(8):e811-e813.
19. Calamia KT, Balabanova M, Perniciaro C, Walsh JS. Livedo (livedoid) vasculitis and the factor V Leiden mutation: additional evidence for abnormal coagulation. *J Am Acad Dermatol*. 2002;46(1):133-137.
20. Kavala M, Kocaturk E, Zindanci I, Turkoglu Z, Altintas S. A case of livedoid vasculopathy associated with factor V Leiden mutation: successful treatment with oral warfarin. *J Dermatolog Treat*. 2008;19(2):121-123.
21. Criado PR, Alavi A, Halpern I, Sotto MN, Kirsner RS. Unilateral livedoid vasculopathy associated with involutional phase of cutaneous infantile hemangioma: the connection to coagulation disorders. *Int J Low Extrem Wounds*. 2013;12(4):306-309.
22. Anavekar NS, Kelly R. Heterozygous prothrombin gene mutation associated with livedoid vasculopathy. *Australas J Dermatol*. 2007;48(2):120-123.
23. Cardoso R, Gonçalo M, Tellechea O, Maia R, Borges C, Silva JA, Figueiredo A. Livedoid vasculopathy and hypercoagulability in a patient with primary Sjögren's syndrome. *Int J Dermatol*. 2007;46(4):431-434.
24. Antunes J, Filipe P, André M, Fraga A, Miltenyi G, Marques Gomes M. Livedoid vasculopathy associated with plasminogen activator inhibitor-1 promoter homozygosity (4G/4G) and prothrombin G20210A heterozygosity: response to t-PA therapy. *Acta Derm Venereol*. 2010;90(1):91-92.
25. Castillo-Martínez C, Moncada B, Valdés-Rodríguez R, González FJ. Livedoid vasculopathy (LV) associated with sticky platelets syndrome type 3 (SPS type 3) and enhanced activity of plasminogen activator inhibitor (PAI-1) anomalies. *Int J Dermatol*. 2014;53(12):1495-1497.
26. Shankar S, Vasudevan B, Deb P, Langer V, Verma R, Nair V. Livedoid vasculopathy—a vasculitic mimic. *Arthritis Rheum*. 2013;65(3):791.
27. Davis MD, Wysokinski WE. Ulcerations caused by livedoid vasculopathy associated with a prothrombotic state: response to warfarin. *J Am Acad Dermatol*. 2008;58(3):512-515.
28. Gotlib J, Kohler S, Reicherter P, Oro AE, Zehnder JL. Heterozygous prothrombin G20210A gene mutation in a patient with livedoid vasculitis. *Arch Dermatol*. 2003;139(8):1081-1083.
29. Brockley J, Recica H, Tso S, Ilchyshyn A. Multiple exquisitely painful leg ulcerations in a teenager. *Br J Dermatol*. 2013; 169:28
30. Morais P, Mota A, Azevedo F, Almeida M. Livedoid vasculopathy with hyperhomocysteinemia: therapeutic approach. *J Am Acad Dermatol*. 2010;62(3):AB26.
31. Sahin N, Kisaarslan AP, Cicek SO, Sözeri B, Akcin ME, Gunduz Z, Dusunsel R, Poyrazoglu MH. Hyperbaric oxygen therapy in a livedoid vasculopathy: A case report. *Pediatr Rheumatol*. 2017;15(Suppl 2):64-65. https://doi.org/10.1186/s12969-017-0185-x.
32. Vázquez MS, Nevarez O, Martin RF. Livedoid vasculopathy (LV) associated with hyperhomocysteinemia due to a homozygous methylene tetrahydrofolate reductase (MTHFR) C677T mutation: a case report. *J Am Acad Dermatol*. 2018;79(3):A178.
33. Wong M, Ramakrishnan R, Teixeira F, Ali I. A case of livedoid vasculopathy associated with a raised factor VIII level: A case report and review of the literature related to coagulation disorders. *Br J Dermatol*. 2011;165:13-14.
34. Devlin AM, Clarke R, Birks J, Evans JG, Halsted CH. Interactions among polymorphisms in folate-metabolizing genes and serum total homocysteine concentrations in a healthy elderly population. *Am J Clin Nutr*. 2006;83(3):708-713.
35. Levin BL, Varga E. MTHFR: addressing genetic counseling dilemmas using evidence-based literature. *J Genet Couns*. 2016; 25(5):901-911.
36. Eriksson P, Kallin B, van 't Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. *Proc Natl Acad Sci U S A*. 1995;92(6): 1851-1855.
37. Hultman K, Tjarnlund-Wolf A, Odeberg J, Eriksson P, Jern C. Allele-specific transcription of the PAI-1 gene in human astrocytes. *Thromb Haemost*. 2010;104(5):998-1008.
38. Ceelie H, Spaargaren-van Riel CC, Bertina RM, Vos HL. G20210A is a functional mutation in the prothrombin gene; effect on protein levels and 3′-end formation. *J Thromb Haemost*. 2004;2(1):119-127.
39. Kujovich JL. Factor V Leiden thrombophilia. *Genetics Med*. 2011;13(1):1-16.
40. Feng S, Su W, Jin P, Shao C. Livedoid vasculopathy: clinical features and treatment in 24 Chinese patients. *Acta Derm Venereol*. 2014;94(5):574-578.
41. Liew SC, Gupta ED. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. *Eur J Med Genet*. 2015;58(1):1-10.
42. Agirbasli M, Goktay F, Peker I, Gunes P, Aker FV, Akkiprik M. Enhanced mRNA expression of plasminogen activator inhibitor-1 in livedoid vasculopathy lesions. *Cardiovasc Ther*. 2017;35(3):e12255. https://doi.org/10.1111/1755-5922.12255.
43. Gao Y, Jin H. Plasminogen activator inhibitor-1: a potential etiological role in livedoid vasculopathy. *Int Wound J*. 2020;17: 1902-1908.
44. Micieli R, Alavi A. Treatment for Livedoid vasculopathy: a systematic review. *JAMA Dermatol*. 2018;154(2):193-202.

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