

Systematic Review

Genetic Contributions to Breast Cancer-Related Lymphedema—Does Subclinical Disease Increase Risk? A Systematic Review

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Abstract

Breast cancer-related lymphedema (BCRL) is a chronic and debilitating complication of breast cancer treatment, commonly associated with mastectomy, axillary lymph node dissection, and adjuvant radiation therapy. Though demographic and treatment-related risk factors for BCRL are well documented, emerging evidence suggests that certain genetic polymorphisms may predispose some patients to developing the condition. This review aims to summarize the current research regarding the genetic variants implicated in the development and severity of BCRL. Several candidate genes related to lymphangiogenesis, inflammation, immune cell activation, and lymphatic contractility have been identified. Unfortunately, the existing literature remains limited by the small number of manuscripts, modest sample sizes, and heterogeneous methodologies of available studies. However, further research may shed light on screening options and lead to more personalized treatment strategies to mitigate the incidence and severity of secondary lymphedema.

Keywords: genetic predisposition; breast cancer-related lymphedema; lymphedema genetics; secondary lymphedema screening; lymphedema physiology

1. Introduction

Breast cancer-related lymphedema (BCRL) is a feared complication of comprehensive breast cancer care. Damaged lymphatic channels allow lymph to pool in the soft tissue, which causes tissue fibrosis in a vicious cycle that leads to progressive swelling, resultant worsening of fibrosis, pain, and disability in the affected limb. While extrinsic intervention and demographic data including axillary dissection, age greater than sixty years, axillary radiation, and obesity have been found to increase risk of BCRL [1], intrinsic genetic predisposition is less commonly described. Identifying candidate genetic profiles that predispose patients to lymphedema could allow for risk stratification and guide patient selection for prophylactic microsurgical and clinical intervention. The present review seeks to report current candidate genetic factors that may contribute to the development of BCRL.



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2. Results

Our initial search across all databases returned 1138 sources. Four hundred of these were duplicates, leaving a total of 738 titles and abstracts to screen. A total of 24 studies were assessed in their entirety, of which 10 did not meet the final inclusion criteria. Five studies were excluded for having outcomes that did not align with genetic risks for BCRL. Two were excluded because their study outcomes did not report genetic profiles. Two additional studies were excluded because they did not investigate genetic predisposition to lymphedema in breast cancer care. One study was excluded because a full text was not available. After completion of screening and full-text review, 14 articles were included [2–15] (see Figure 1). Of these 14 articles, 9 were human studies, and the remaining 5 utilized animal models. Our search identified a body of research working to isolate target genes that may have the potential to stratify baseline genetic risk for BCRL. Results suggest that direct genetic inquiry in this area is relatively new, with included study publication dates ranging from 2008 to 2025.

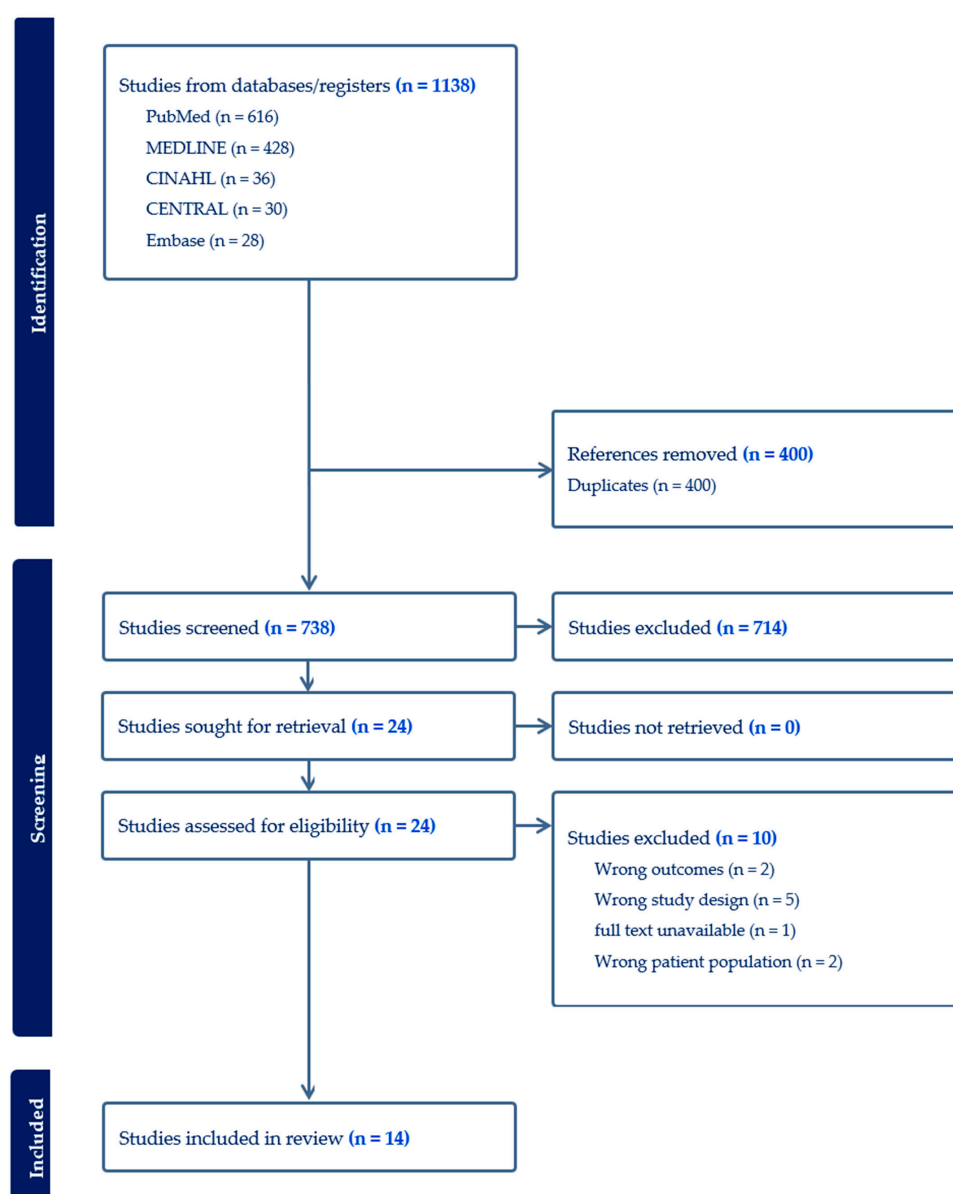


Figure 1. PRISMA diagram. Shows the PRISMA-organized results of the literature review.

A total of 29 unique genetic factors were identified. In total, 7 were associated with lymphatic structure and development, 14 with inflammation and immunological response to injury, 3 with immune activation and adhesion, and 1 cluster of genes associated with lymphatic function and contractility (see Table 1). To support transparent evaluation of the evidence base, the key methodological characteristics of the included studies are summarized in Table 2 to allow the readers to assess the relative strength and comparability of each investigation.

Table 1. Relevant genes and their functional classifications.

Gene	Function	Reference
Connexin Isoforms	Lymphatic Structure and Development	Davis et al. 2025 [14], Hadizadeh et al. 2018 [13], Finegold et al. 2012 [15]
Vascular Endothelial Growth Factor (VEGF)	Lymphatic Structure and Development	Newman et al. 2012 [2], Miaskowski et al. 2013 [7], Fu et al. 2016 [10]
Forkhead Box Protein C2 (FOXC2)	Lymphatic Structure and Development	Newman et al. 2012 [2], Miaskowski et al. 2013 [7]
Prospero Homeobox 1 (PROX1)	Lymphatic Structure and Development	Newman et al. 2012 [2], Hespe et al. 2019 [9]
SYR-Box Transcription Factor (SOX18)	Lymphatic Structure and Development	Newman et al. 2012 [2]
Lymphatic Vessel Endothelial Hyaluronan Receptor 1 (LYVE1)	Lymphatic Structure and Development	Newman et al. 2012 [2]
Adrenomedullin (ADM)	Lymphatic Structure and Development	Newman et al. 2012 [2], Nikitenko et al. 2013 [6]
Hepatocyte Growth Factor/Mesenchymal Epithelial Transitional Tyrosine Kinase (HGF/MET)	Lymphatic Structure and Development	Finegold et al. 2008 [5]
Neuropilin-2	Lymphatic Structure and Development	Miaskowski et al. 2013 [7]
GATA Binding Protein 1 (GATA2)	Lymphatic Structure and Development	Watanabe-Asaka 2024 [11]
IL4	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10], Leung et al. 2014 [4]
IL10	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Leung et al. 2014 [4], Fu et al. 2016 [10]
IL2	Inflammation and Immune Response	Miaskowski et al. 2024 [3]
IL17A	Inflammation and Immune Response	Miaskowski et al. 2024 [3]
IL1	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10]
IL6	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10]
IL13	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10]
C-X-C Motif Chemokine Ligand 8 (CXCL8 (Formerly IL-8))	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10]
RAR Related Orphan Receptor C (RORC)	Inflammation and Immune Response	Newman et al. 2012 [2]
Interferon Gamma (IFNG)	Inflammation and Immune Response	Miaskowski et al. 2024 [3]
IFNG Receptor 1	Inflammation and Immune Response	Miaskowski et al. 2024 [3]
Tumor Necrosis Factor (TNF)	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Fu et al. 2016 [10]
Nuclear Factor Kappa Beta (NFKB)	Inflammation and Immune Response	Miaskowski et al. 2024 [3], Leung et al. 2014 [4]
Toll-Like Receptor (TLR)	Inflammation and Immune Response	Zampell et al. 2012 [12]
Lymphocyte Cytosolic Protein 2 (LCP2)	Immune Cell Activation and Adhesion	Miaskowski et al. 2013 [7]
Spleen Tyrosine Kinase (SYK)	Immune Cell Activation and Adhesion	Miaskowski et al. 2013 [7]
Vascular Cell Adhesion Molecule 1 (VCAM-1)	Immune Cell Activation and Adhesion	Miaskowski et al. 2013 [7]
Voltage-Gated Potassium Channels	Function and Contractility	Smoot et al. 2017 [8]

Table 2. Summary of key methodological features of the included manuscripts.

Source	Gene Variants Investigated	Sample Size	Study Type	Clinical Outcomes
Newman et al. 2012 [2]	<i>SOX18, VEGFC, VEGFD, VEGFR2, VEGFR3, RORC, FOXC2, LYVE1, ADM, PROX1</i>	120	Case-control	Polymorphisms in <i>VEGFR2</i> , <i>VEGFR3</i> , and <i>RORC</i> found to be associated with lymphedema
Miaskowski et al. 2024 [3]	<i>CXCL8, IFNG, IFNG1, IFNGR1, IL1R1, IL1R2, IL2, IL4, IL6, IL17A, IL1B, IL10, IL13, IL17A, NFKB1, NFKB2, TNFSF</i>	155	Observational (cross-sectional and longitudinal)	Polymorphisms in <i>IL1B</i> and <i>IL6</i> found to be associated with increased lymphedema severity
Leung et al. 2014 [4]	<i>IFNG1, IFNGR1, IL1B, IL1R1, IL1R2, IL2, IL4, IL6, IL8, IL10, IL13, IL17A, NFKB1, NFKB2, TNFA</i>	542	Observational (cross-sectional and longitudinal)	Polymorphisms in <i>IL4</i> , <i>IL10</i> , and <i>NFKB2</i> associated with inflammatory responses in the development of lymphedema
Finegold et al. 2008 [5]	<i>HGF, MET</i>	239	Case-control	Mutations in <i>HGF</i> and <i>MET</i> found to contribute to lymphedema
Nikitenko et al. 2013 [6]	<i>ADM</i>	Not specified	In vivo experimental study	Reduced adrenomedullin levels increase susceptibility to secondary lymphedema
Miaskowski et al. 2013 [7]	<i>ANGPT2, FOXC2, HGF, LCP2, LYVE1, MET, NRP2, PROX1, RORC, SOX17, SYK, VCAM1, VEGFB, VEGFC, VEGFD, VEGFR2, VEGFR3</i>	543	Observational (cross-sectional and longitudinal)	Polymorphisms in <i>LCP2</i> , <i>NRP2</i> , <i>SYK</i> , <i>VCAM1</i> , and three haplotypes (<i>FOXC2</i> A03, <i>NRP2</i> F03, <i>VEGFC</i> B03) associated with lymphangiogenesis and angiogenesis
Smoot et al. 2017 [8]	<i>KCNA1, KCND2, KCNS1, KCNJ3, KCNJ5, KCNJ6, KCNJ9, KCNK2, KCNK3, KCNK9</i>	542	Observational (cross-sectional and longitudinal)	Polymorphisms in <i>KCNA1</i> , <i>KCNJ3</i> , and <i>KCNJ6</i> , and <i>KCNK3</i> associated with lymphedema
Hespe et al. 2019 [9]	<i>Prox1</i>	Not specified	In vivo experimental study	Subclinical lymphatic dysfunction intensifies the effects of lymphatic injury
Fu et al. 2016 [10]	<i>VEGF-C, VEGF-D, IL1-α, IL-4, IL6, IL8, IL10, IL13, TNF-α</i>	140	Prospective cohort (genetic association)	Polymorphisms in <i>IL4</i> contribute to impaired limb mobility, polymorphisms in <i>IL6</i> and <i>IL4</i> contribute to fluid accumulation, and polymorphisms in <i>VEGF-C</i> and <i>IL-13</i> contribute to patient discomfort
Watanabe-Asaka et al. 2024 [11]	<i>GATA2</i>	Not specified	In vivo experimental study	Placement of soluble type I collagen significantly improved lymphatic recanalization in <i>GATA2</i> heterozygous-deficient mice, suggesting a potential therapeutic strategy for <i>GATA2</i> -related lymphedema
Zampell et al. 2012 [12]	<i>TLR2, TLR4, TLR9, VEGF-A, VEGF-C, LYVE-1</i>	Not specified	In vivo experimental study	Loss of TLR signaling (<i>TLR2</i> , <i>TLR4</i> , <i>TLR9</i>) in mice impairs lymphatic repair and lymphangiogenesis
Hadizadeh et al. 2018 [13]	<i>GJA4</i>	102	Retrospective case-control	Polymorphisms in <i>GJA4</i> associated with an increased risk of secondary lymphedema
Davis et al. 2025 [14]	<i>GJA4, GJA1, GJC1, GJC2</i>	Not specified	In vivo experimental study	4 connexin isoforms (Cx37, Cx47, Cx43, Cx45) contribute to lymphatic valve function, and polymorphisms in <i>GJA4</i> predispose to lymphedema
Finegold et al. 2012 [15]	<i>GJC2, FOXC2, HGF, MET, FLT4</i>	188	Case-control study with in vitro functional validation	Polymorphisms in <i>GJC2</i> implicated in impaired lymphatic gap junctions

3. Discussion

3.1. Genes Impacting Lymphatic Structure and Development

Connexins are a class of proteins that play a role in lymphangiogenesis embryologically and coordinate migration and elongation of lymphatic endothelial cells to form intraluminal valve leaflets, which prevent backflow and stasis of lymphatic fluid [16]. A 2025 investigation into lymphatic-specific connexins in a mouse model (Cx37, Cx47, Cx43, and Cx45) found that Cx37 and Cx45 haploinsufficiency had the greatest impact on the development of subclinical embryologically flawed lymphatic vessels with significantly higher backflow and worse competence compared to wild type [14]. Two previous investigations found significantly increased baseline risk of BCRL in patients with Cx47

polymorphisms and suggest that possible inherited abnormalities in lymphatic structure and function may predispose patients to secondary lymphedema [13,15]. Finegold's 2012 investigation did not completely control for environmental factors and found higher rates of connexin mutation in the cohort affected by BCRL, but this group was significantly older, had significantly more lymph nodes removed at their index procedure, and had higher rates of post-operative radiation [15]. In 2018, Hadizadeh et al. undertook a cohort study that controlled for these and presented two cohorts with no significant underlying demographic or treatment differences and still found a statistically significant relationship between connexin 37 mutation and BCRL [13].

Vascular endothelial growth factor (*VEGF*) is a primary growth factor in lymphangiogenesis in infancy and adulthood. It is a chemotactic agent that attracts monocytes and macrophages, which release additional growth factors and participate in the formation of lymphatic channels [17]. Mutations in *VEGF* and its downstream pathways were identified in three studies, with two finding significant associations with the development of BCRL [2,7]. Fu et al. in 2016 did not detect a statistically significant increase in risk of developing BCRL based on *VEGF* mutations in their cohort; however, this study had a small total prospective cohort of 140 patients with 16% developing lymphedema [10].

SRY-box transcription factor 18 (*SOX18*) is another crucial embryologic growth factor that plays a role in the differentiation of lymphatic endothelial precursor cells and has been implicated in driving lymphatic metastatic spread in some solid tumors [18,19]. Newman et al. did not detect a significant association between *SOX18* polymorphisms and BCRL [2]. Likewise, the group also investigated lymphatic vessel endothelial hyaluronan receptor 1 (*LYVE1*) and *neuropilin-2*, which are also associated with malignant lymphangiogenesis, and did not find a significant association between genetic isoforms and the development of BCRL [2,20,21].

Forkhead Box C2 (*FOXC2*) is upregulated during lymphatic development and interacts with *PROX1* to form lymphatic and venous valve structures embryologically and maintain them throughout development and adult life [22]. Newman et al.'s 2012 study did not detect a significant increase in risk of BCRL among isoforms of *FOXC2*; however, Miaskowski et al. did detect a small increase in risk in a larger sample, but noted that functional studies of the SNP haplotypes they identified would be needed to show a true association [2,7]. Clinical studies have shown that *PROX1* has minimal evidence of clustering and did not significantly impact the risk of development of BCRL in a human cohort [2]. While no clinical association in human cohorts was found in the present review, *PROX1*-haploinsufficient mice did demonstrate leakier lymphatics, increased local inflammation, and worse pumping mechanics following lymphatic insult [9].

Adrenomedullin (AM) is a peptide hormone in the same family as calcitonin gene-related peptide (CGRP) that contributes to vasodilatory responses and lymphatic formation through a downstream cyclic adenosine monophosphate pathway [23]. A 2013 animal study by Nikitenko et al. found that deficiency of functional AM, even in the presence of healthy receptors, led to increased hind-limb circumference in an adult mouse model of lymphatic injury [6]. AM polymorphisms were not found to differ significantly between patients who developed BCRL and those who did not in Newman et al.'s 2012 study [2].

Finegold et al. noted that Hepatocyte Growth Factor (*HGF*) and its high-affinity receptor Mesenchymal Epithelial Transitional Tyrosine Kinase (*MET*) had a similar frequency of mutation in affected individuals as several other implicated genes in their 2008 study. However, no statistical investigation was undertaken, and no other identified studies investigated this relationship [5].

Lymphatic extracellular matrices have also been implicated in disease development in BCRL. GATA-binding transcription factor (*GATA2*) heterozygous-deficient mice demon-

strated more tightly packed collagen around damaged lymph vessels in a 2024 mouse model investigation [11]. It was noted that aberrant fibroblast collagen deposition created a dense environment that hindered lymphatic healing [11]. Additionally, reintroduction of wild-type soluble collagen allowed for healthy recanalization and suggests that stiffness of extracellular scaffolding around healing lymphatics could contribute to disease development and progression [11].

3.2. Inflammatory and Immunological Genes

A number of interleukin gene variants were evaluated in the human studies included in this review. Polymorphisms in pro-inflammatory interleukins IL-1 [3,10], IL-6 [3,10], and IL-13 [10] were associated with increased risk of BCRL. No associations were found for CXCL8 (formerly IL-8) [3,10] or IL17A [3]. Anti-inflammatory interleukin associations were also evaluated for IL-4 [4] and IL-10 [4], with studies identifying variants of each that were significantly associated with increased risk of development of BCRL. The studies investigating these inflammatory mediators did not consistently identify risks associated with polymorphisms in these genes, with some cohorts detecting no risk in gene variants that others did. Inflammatory pathways undoubtedly contribute to lymphedema, but these results do not identify a particular aberration that leads to BCRL but rather strengthen evidence that inflammation plays a critical role in the development and morbidity of lymphedema.

RAR Related Orphan Receptor C (*RORC*) has been associated with lymphoid organ development in animal studies and plays a role in activation of IL-2 transcription [24]. Single-nucleotide polymorphisms of this gene were found to be significantly associated with lymphedema development in a single study. The authors hypothesized that the implicated SNPs have altered transcription factor binding sites, which may affect the activity of the gene product and could alter inflammatory activity at sites of injury in affected patients [2].

Nuclear factor kappa beta (*NFKB*) is a transcriptional regulator involved in angiogenesis, apoptosis, cell proliferation, and inflammation. Leung et al. reported a single, rare allele of the gene that was associated with a 3.1-fold increased risk of development of BCRL [4]. These findings were supported by additional clinical demonstrations of increased risk of development of BCRL based on *NFKB* polymorphisms [3].

Interferon Gamma (*IFNG*) is a non-specific excitatory cytokine that acts as an early reactant in infection and the inflammatory cascade. Both ligand and receptor genes for *IFNG* were investigated by Miaskowski et al. in 2024, with no association found between genetic polymorphism and development of BCRL [3]. This group and Fu et al.'s 2016 study also tested associations between tumor necrosis factor (*TNF*) polymorphisms, another pro-inflammatory mediator, and likewise found no association linking it to BCRL [10].

Toll-like receptors (TLRs) are proteins that participate in the innate immune response and activate inflammatory and immunogenic signals when they bind to pathogen-associated molecular patterns that are foreign to an organism. A 2011 investigation showed that mice with TLR knockouts for TLR-2, TLR-4, or TLR-9 all demonstrated significantly increased tail circumference after tail lymph node excision compared to wild-type mice. The authors propose that decreased macrophage and local inflammatory responses to injury decrease the animals' ability to induce lymphangiogenesis [12]. They also found that TLR deficiency was associated with increased concentrations of tightly packed type I collagen in the extracellular matrix, which may impede lymphatic growth and organization [12].

3.3. Immune Cell Activation and Adhesion Genes

In Miaskowski et al.'s 2013 polygenic investigation, they included three genes that participate in inflammatory activation, adhesion, and migration and found that lympho-

cyte cytosolic protein 2 (*LCP2*), spleen tyrosine kinase (*SYK*), and vascular cell adhesion molecule-1 (*VCAM-1*) polymorphisms were all significant risk modifiers for the development of BCRL [7]. The pathophysiology of lymphedema can be traced in part to dysfunction of immune cell adhesion to lymphatic endothelium, thereby compromising clearance of protein-rich interstitial fluid and microenvironmental debris. Upregulation of *VCAM1* typically mediates monocyte and lymphocyte adherence to endothelium. Polymorphic variations to this transmembrane sialoglycoprotein may attenuate or exaggerate the adhesion mechanism. Miaskowski and colleagues showed that variation in SNP rs3176861 of the *VCAM1* gene was shown to be significantly associated with the modulation of lymphedema [7]. Likewise, a regression analysis by Miaskowski et al. showed that carrying two copies of the for *SYK* rs158689 allele was associated with nearly a 3.5-fold increase in the odds of developing lymphedema [7]. They also found that a single nucleotide polymorphism in *SYK* was able to explain up to ~3% of the variance in lymphedema risk [7]. This may be due to the central role of *SYK* in the activation and integrin signaling of B-cells, T-cells, and myeloid cells. Genetic perturbations in *SYK* may result in a milieu that impedes lymphangiogenesis and lymphatic remodeling due to a shift in the balance between adaptive immune resolution and chronic low-grade inflammation.

The group's regression analysis for *LCP2* rs315721 was also able to explain 18.9% of the variance for the odds of developing lymphedema [7]. *LCP2* contributes to lymphatic vessel development by modulating hematopoietic signaling pathways that control the separation of the blood and lymphatic networks. In this pathway, *SYK* interacts as an upstream kinase for the downstream adaptor molecule *LCP2*. Together, these molecules comprise a portion of the core regulatory axis essential for maintaining vascular segregation. A single genetic variation in either gene could disrupt the coordinated signaling between *SYK* and *LCP2*, leading to a potential alteration within the cascade that ensures proper vascular compartmentalization.

Miaskowski et al. provide compelling data to support the notion that the risk for developing lymphedema can be attributed in part to polymorphisms in adhesion and immune-signaling genes. These findings suggest that altered endothelial-immune cell interaction may impair lymphatic recovery or promote maladaptive remodeling in the post-operative setting of breast cancer treatment, thus prompting further consideration of immune activation and adhesion genes as potential modulators and therapeutic targets in treatment strategies aimed at lymphedema prevention and management.

3.4. Function and Contractility

Lymphatic pump activity is largely driven by the potassium gradient across lymphatic smooth muscle cell membranes. The movement of K⁺ channels across the cell membrane maintains the resting membrane potential, allowing action potentials to fire and trigger smooth muscle contraction and subsequent lymphatic flow [25].

The mechanism by which K⁺ channel dysfunction leads to the development of BCRL likely begins with impaired K⁺ channel activity leading to contractile dysfunction and subsequent loss of pulsatile lymphatic flow in patients with loss-of-function K⁺ channel variants. This results in endothelial barrier dysfunction mediated by myosin light chain phosphorylation, promoting the accumulation of protein-rich interstitial fluid that creates a pro-inflammatory microenvironment [26,27]. Combined with mechanical stress from edema, this triggers inflammatory pathways that potentiate profibrogenic mechanisms within fibroblasts, causing increased collagen deposition and progressive fibrosis of lymphatic channels [27]. Collectively, this establishes a positive feedback loop in which progressive fibrosis further impairs lymphatic flow and perpetuates disease progression [27].

A single investigation by Smoot et al. in 2017 demonstrated that polymorphisms in potassium channels that play a major role in lymphatic contractility increased the risk of developing BCRL [8]. KCNA1 encodes for components of the K⁺ voltage-gated channel, which is responsible for the hyperpolarization of the cell membrane and the return of the membrane to its resting state. Two genes, KCNJ3 and KCNJ6, encode for components of the G-protein inwardly rectifying potassium channels, which work to stabilize the cell's resting potential by promoting an influx of potassium current into the cell. KCNK3 encodes part of the two-pore K⁺ channel, which establishes potassium leak currents necessary for the maintenance of the membrane's resting potential. Polymorphisms in these genes may therefore enhance or disrupt lymphatic smooth muscle contraction and lead to altered lymphatic drainage. The study identified six such polymorphisms across these four genes that were found to be significantly associated with BCRL: KCNA1 rs4766311, KCNK3 rs1662988, KCNJ3 rs1037091, KCNJ6 rs2211845, KCNJ6 rs991985, and KCNJ6 rs2836019. Of these, all were associated with a decreased likelihood of developing secondary lymphedema except for KCNJ6 rs2211845 and KCNJ6 rs991985, which were associated with increased odds [8].

3.5. Limitations

The present study sought to amalgamate the current state of the literature regarding genetic predisposition to BCRL. The heterogeneity of findings, numerous genes implicated in disease, and differences in study design unfortunately preclude meta-analytics at this time, which would significantly strengthen any recommendations that could be made based on the presented findings.

Measurement of lymphedema and diagnostic criteria to identify patients and disease differed among the presented studies. Hind limb swelling and lymphatic uptake of Evans blue were utilized by Nikitenko et al. and Watanabe-Asaka et al. [6,11]. Zampell's work created a lymphedematous state using a tail injury model of lymphedema, which is commonly employed in the literature [12,28]. Hespe utilized lymphoscintigraphy in the included experimental animals to diagnose lymphedema [9]. Davis et al.'s investigation into valve function in connexin-mutated mice directly measured valve backflow and leaflet gap dimensions at the bench to determine the effects of the included genes on valve dynamics [14]. Bioimpedance resistance ratios were used by Smoot et al., Leung et al., and in both reports by Miaskowski et al. [3,4,7,8]. Measurement of arm circumference via tape measure or via infrared perometry was described as well [2,10,29]. Physician diagnosis and International Society of Lymphology criteria were utilized in some cohorts as well [5,13,15]. Inconsistent diagnostic criteria may impact probands included in analytics and could affect reported results.

4. Materials and Methods

4.1. Eligibility Criteria

Human and animal studies that included genetic analysis to determine an association of the expression of a protein or gene with the development of BCRL were selected for inclusion. Studies unavailable in English, reviews, conference abstracts, and book chapters were excluded.

4.2. Search Strategy

A computerized search was conducted on 18 August 2025, by the first and second authors independently from 1975 to August 2025 using PubMed, Embase, CINAHL, CENTRAL, and MedLine. The following MeSH terms were used: genetic predisposition, genetic variant, polymorphism, mutation, SNP, germline susceptibility, inherited risk, genomic

risk, lymphedema, cancer-associated lymphedema, secondary lymphedema, breast cancer-related lymphedema, and breast cancer-associated lymphedema.

4.3. Study Review and Data Collection

Two researchers independently searched and filtered studies based on titles and abstracts using the inclusion and exclusion criteria described above. Full-text articles were then reviewed for relevance and content. Articles were excluded if the study design did not meet the above criteria. If no agreement could be reached, a third senior author designated whether the article should be included or excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was the basis of our organization [30].

5. Conclusions

BCRL is a complex, likely polygenic disease process. The present study suggests that a number of subclinical phenotypic manifestations of subtle genetic mutations may predispose patients to the development of BCRL. Our investigation was limited by a relatively small number of manuscripts that met strict inclusion criteria, but it is strengthened by our standardized search and screening approach. Inflammatory mediators were commonly implicated but may represent nonspecific contributions to the development of lymphedema. Subclinical lymphatic dysfunction caused by intrinsic genetic alteration in genes associated with the structure and development of lymphatics leverages promising potential preoperative screening tools for patients who require mastectomy for breast cancer or prophylaxis. A prospective clinical trial collecting genetic data from patients prior to operative intervention to evaluate their genotype and monitor the development of BCRL, based on the presented results, could begin to shape effective genetic screening. Such risk stratification may directly inform prophylactic surgical and perioperative risk-reducing strategies for secondary lymphedema. Individuals with high-risk genotypes could be considered for adjunct surgical procedures such as prophylactic lymphaticovenular anastomosis or the lymphatic microsurgical preventive healing approach (LYMPHA). These patients may also benefit from enrollment in structured prospective surveillance programs, early intervention compression protocols, and immediate post-operative physiotherapy or manual lymphatic drainage to support lymphatic flow and shoulder mobility. As high-risk patients become identifiable prior to surgery, future research can help determine which interventions most effectively preserve function and optimize quality of life after mastectomy.

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