JPRAS Open 44 (2025) 529–541

Contents lists available at ScienceDirect

JPRAS Open

journal homepage: www.elsevier.com/locate/jpra

Review Article

Genetic variants in the development of autoimmune complaints and capsular contracture in women with breast implants: A systematic review

Alan González[a,*], Daniela Quibano-Ordoñez[b,d], Laura Ortega-Muñoz[b], Pedro A. Moreno[c], Patricia E. Vélez-Varela[d]

[a] *Esp. CareMe 360 Institute S.A.S. Barranquilla, COLOMBIA*
[b] *Integrim S.A.S. Bogotá DC, COLOMBIA*
[c] *EISC, Faculty of Engineering. Universidad del Valle. Cali, COLOMBIA*
[d] *Department of Biology, FACNED, Universidad del Cauca, Popayán, COLOMBIA*

ARTICLE INFO

Article history:
Received 16 August 2024
Accepted 6 April 2025
Available online 15 April 2025

Key words:
Capsular contracture
genetic markers
autoimmune diseases
breast implants

ABSTRACT

Introduction: Breast implants were introduced in 1963 by Cronin and Gerow and are widely used for reconstructive and aesthetic purposes. However, their use has been controversial due to the potential risk of developing autoimmune diseases and surgical complications such as capsular contracture. Currently, no genetic markers have been identified that are definitively associated with these complications. Therefore, we conducted a systematic review to check for the presence of genetic variants that are related to complications such as capsular contracture and autoimmune diseases in women with breast implants.

Materials and Methods: A systematic review was conducted following the preferred reporting items for systematic reviews and meta-analyses guidelines. The search included databases such as Web of Science, PubMed, and Scopus, using terms such as “breast implants,” “breast prostheses,” “genes,” “genetic markers,” and “au-

* Correspondence concerning this article should be addressed to: Alan González, MD, CareMe 360 Institute S.A.S, CR 53 #82-86, Edificio Ocean Towers, Barranquilla, COLOMBIA.

E-mail addresses: dr.alangonzalezmd@gmail.com (A. González), coordinacioninvestigacion@alangonzalez.com (D. Quibano-Ordoñez), direccionmedicadeinvestigacion@alangonzalez.com (L. Ortega-Muñoz), pedro.moreno@correounivalle.edu.co (P.A. Moreno), pvelez@unicauca.edu.co (P.E. Vélez-Varela).

https://doi.org/10.1016/j.jpra.2025.04.007

toimmunity." The selected studies were cross-sectional, cohort, and case-control studies that assessed specific genetic variants in women with breast implants and their association with autoimmune diseases or capsular contracture.

Results: A total of 6 cross-sectional studies and 1 case-control study were included. The findings related to autoimmune diseases showed a high prevalence of the HLA-DQ10102 variant among women with myositis associated with breast implants compared to women with myositis without implants (81.8% vs. 31.6%; OR 9.8, 95% CI 1.77–96.79). Other studies identified genetic variants associated with capsular contracture, highlighting the expression of MMP, TIMP, TNF-α, and IL-8 genes in severe contractures.

Conclusion: Prolonged inflammation and specific genetic variants play a crucial role in the development of capsular contracture and autoimmune diseases in women with breast implants. Identifying these genetic markers could help improve the prediction and management of these complications. However, more longitudinal studies are needed to better understand the mechanisms and validate these findings.

Introduction

Breast implants are devices used for reconstructive and aesthetic purposes; they were first introduced in 1963 by Cronin and Gerow.[1] Breast augmentation is the second most performed procedure in plastic surgery worldwide. According to statistics from the International Society of Aesthetic Plastic Surgery, 2,174,616 breast augmentation surgeries were performed in 2022, which generally involved the use of implants. In Colombia, 63,204 breast augmentation surgeries were performed in 2022, making it the second most popular procedure of the year.[2] Approximately 50 million women worldwide have breast implants.[3]

Breast implants have been controversial owing to the possible risk of developing autoimmune diseases. Watad et al. found significant associations between implants and autoimmune diseases such as sarcoidosis (OR 1.95, 95% CI 1.27–2.99), multiple sclerosis (OR 1.64, 95% CI 1.16–2.32), and Sjögren's syndrome (OR 1.61, 95% CI 1.15–2.26).[4] HLA complex genes, known for their association with autoimmune diseases, might be involved in the relationship between silicone implants and these conditions. Haplotypes such as HLA-DRB1 and HLA-DQ alleles in patients with silicone implants may be related to the development of autoimmunity.[5] However, specific genes that could serve as susceptibility markers that link silicone implants to the development of autoimmune diseases are yet to be identified.

Moreover, there are surgical complications such as implant rupture and capsular contracture.[6] The latter is a condition where the scar tissue that forms around an implant (periprosthetic capsule) hardens, potentially causing pain and a distorted aesthetic appearance. By itself, the capsule is a normal bodily reaction.[7] However, during capsule formation, inflammatory cells such as neutrophils, macrophages, and T cells release cytokines such as TNF-α (tumor necrosis factor), interleukin 1 (IL-1), IL-6, IL-8, IL-10, and transforming growth factor (TGF-β), which can be associated with contracture development.[8] Currently, no marker has been directly confirmed to be associated with the severity of capsular contracture, because of which we proposed a systematic review to check for the presence of genetic variants that may be related to complications such as capsular contracture and autoimmune disease in women with breast implants.

Materials and methods

This review was conducted according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[9] This systematic review was not registered with any prospective registry. Owing to the heterogeneity of the topics covered in the included studies, it was not possible to perform any analysis beyond a qualitative synthesis.[10]

Searching strategy

During June 2024, an exhaustive review of the research was conducted using controlled language and keywords in the Web of Science, PubMed, and Scopus databases. The search terms included "breast prostheses," "silicone implants," "gene," "genetic markers," "chromosomal markers," "biomarkers," "biological markers," "immunological markers," "polymorphisms," "autoimmunity," "immune response," "HLA," and "autoimmune disease" in various combinations using Boolean operators such as "AND" and "OR." The retrieved articles were screened using the following criteria: (i) cross-sectional, cohort, or case-control studies, (ii) studies involving women with breast implants, (iii) studies evaluating specific genetic variants, (iv) studies reporting on autoimmune diseases and/or capsular contracture, and (v) studies in Spanish and English. Letters, editorials, comments, reports, previous systematic reviews, studies not reporting genetic markers, or those associated with cancer were excluded.

Study selection

The search results were independently reviewed by 2 authors using the Rayyan tool.[11] A two-stage selection process was conducted for the selection of studies. First, duplicate studies were removed, and then titles and abstracts were screened according to the inclusion and exclusion criteria. A third reviewer moderated any discrepancies and resolved conflicts. Subsequently, a full-text analysis was performed. If conflicts arose among the reviewers, a third reviewer moderated the discussion to reach a joint decision.

Data extraction

A standardized format was used to extract important information such as study design, sample size, population characteristics, intervention or exposition, comparator, outcome measure, main outcomes, and limitations (Table 1). The content was organized into several sections for a structured presentation. These sections covered the following topics: Genetic variants and autoimmunity, and genetic variants and capsular contracture.

Methodological quality assessment

Quality assessment was carried using the JBI for appraisal assessment for case-control and cross-sectional studies.[2] Each study was rated by assigning scores to each question. Studies scoring $\geq$75% were considered as high quality, those scoring between 50% and 74% were considered as medium quality, and those scoring $<$50% were considered low quality. High-quality evidence included studies with a low risk of bias, medium-quality evidence comprised of studies with a medium risk of bias, and low-quality evidence consisted of studies with a high risk of bias.

Results

After the systematic search, 6 cross-sectional and 1 case-control study were included. The total number of patients were 224. These studies examined the role of autoimmunity and presence of capsular contracture. The most frequent country of origin was United Kingdom (n=3), followed by Germany (n=1), United States (n=1), China (n=1), and Italy (n=1). The PRISMA flowchart provides the details regarding the selection process (Figure 1).

Table 1
Summary of the studies

Study ID	Study type	Population			Intervention / Exposure	Comparator	Outcome measure	Main Outcomes	Limitations
		Country	Sample size	Age, years mean/RNG					
(O'Hanlon et al., 2004)	Case-control	United States	87	52.5 / (36 – 77)	Women with myositis after BI (MASI)	Women with Myositis without BI (IMM) and women with BI without myositis (SIC)	HLA differential expression	All the analysis showed higher HLA DQA1*0102 in MASI MASI vs. IMM (OR 2.6, 95% CI 1.25–5.46) MASI vs. SIC (OR 2.4, 95% CI 1.18– 5.11)	Size bias. No control of cofounder factors.
(D'Andrea et al., 2007)	Cross-sectional	Italy	60	NR / 25 – 45	Patients with CC grade III and IV	Patients with CC grade I and II	Changes in the cysLT gene and TNF expression in macrophages and fibroblast of breast capsules	CysLTR2 and TNF higher ($p < 0.05$) on CC III and IV vs controls	Size bias. No control of cofounder factors.
(Ulrich et al., 2009)	Cross-sectional	Germany	40	27 / NR	Patients with smooth or textured implants and CC grade II, III or IV	Patients with smooth or textured implants and CC grade I	Expression of IMP-1, TIMP-2, MMP-2 y MMP-9 genes	Higher MMP-2 CC II y III/IV if textured BI vs. CC I ($p < 0.05$). Increased expression of TIMP-1 and TIMP-2 in Baker II y III/IV in smooth and textured BI ($p < 0.05$).	Size bias. No control of cofounder factors.
(Tan et al., 2010)	Cross-sectional	UK	7	42.2 / 27 – 61	Patients with CC grade III and IV	Patients with CC grade I and II	Expression of COL3A1, TNF alfa, TGF-beta 1 and CTGF genes.	Positive correlation between TNF-alfa and CC ($r = 0.558$; $p = 0.02$) Negative correlation between COL3A1 and CC ($r = -0.490$; $p = 0.05$).	Size bias. No control of cofounder factors.
(Tan et al., 2011)	Cross-sectional	UK	7	42.2 / 27 – 61	Patients with CC grade III and IV	Patients with CC grade I and II	Genetic expression of TSG-6. Stain intensity of HA, TSG-6, HC1, HC2.	CC had lower HA ($r = -0.645$, $p < 0.001$) and TSG-6 ($r = -0.642$, $p = 0.002$). Age of implant had lower HA ($r = -0.662$, $p < 0.001$) and TSG-6 ($r = -0.619$, $p = 0.004$)	Size bias. No control of cofounder factors.

(*continued on next page*)

Table 1 (*continued*)

Study ID	Study type	Population			Intervention / Exposure	Comparator	Outcome measure	Main Outcomes	Limitations
		Country	Sample size	Age, years mean/RNG					
(Kyle et al., 2013)	Cross-sectional	UK	23 capsules from 18 women.	48,7 / 27–73	Patients with CC grade III and IV	Patients with CC grade I and II	Microarrays. qRT-PCR para 6 genes clave: ACAN, IL8, SAA1, MMP12, TIMP4, TNFSF11.	257 genes dysregulated on CC III and IV ($p<0.05$). qRT-PCR analysis showed IL8 increased on CC III and IV ($p = 0.016$); ACAN and TIMP4 decreased in CC III ($p = 0.002$) and IV ($p = 0.009$). Immunohistochemical analysis IL8 and MMP12 expressed higher on CC III y IV ($p = 0.033$ y $p = 0.037$, respectively); TIMP4 had lower expression on CC III and IV ($p = 0.039$).	Size bias. No control of cofounder factors.
(Mao et al., 2024)	Cross-sectional	China	15 capsules from 12 women	NR	Patients with CC grade III and IV	Patients with CC grade I and II	Genes related with lipidic metabolism and immune response and candidate genes.	The candidate gene was PRKAR2B which showed a positive correlation with M1 macrophages ($r = 0.86$, $P < 0.05$) and follicular helper T cells ($r = 0.86$, $P < 0.05$). Higher expression in CC I and II than in III and IV.	Size bias. Selection bias.

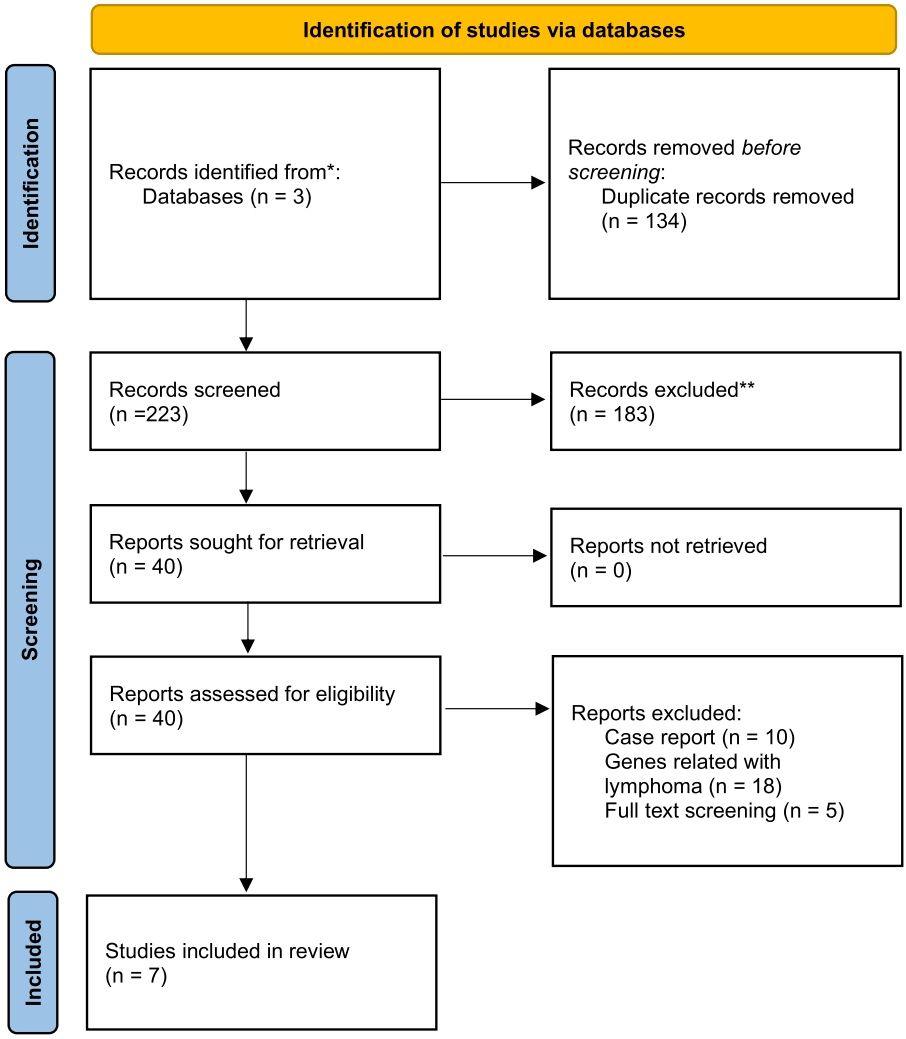

Figure 1. PRISMA flowchart 2020 for systematic reviews

Quality assessment

The JBI tool was used to assess the potential bias of the 7 selected studies. According to the evaluation, the sources of bias included the identification of confounding factors or potential biases and lack of strategies to mitigate them. Based on the assessment, 5 of the 7 studies were of medium quality and only 2 were of high quality. None of the studies were excluded. The results are shown in Table 2.

Description of the studies

Genetic variants and autoimmunity

In this systematic review, a case-control study was selected that investigated the genetic variants associated with autoimmune disease in women with breast implants. O'Hanlon et al. (2004) initially determined a high prevalence of the HLA-DQ10102 variant in women with silicone implant-associated

Table 2
Quality Assessment based on Joanna Briggs Institute Risk of Bias Tool (https://jbi.global/critical-appraisal-tools)

No	Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	RISK OF BIAS
Case – control studies												
1	(O'Hanlon et al., 2004)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Cross-sectional studies												
2	(D'Andrea et al., 2007)	Y	Y	Y	Y	N	N	Y	Y	-		LOW
3	(Ulrich et al., 2009)	U	Y	Y	Y	N	N	Y	Y	-		MEDIUM
4	(Tan et al., 2010)	U	Y	Y	Y	N	N	Y	Y	-		MEDIUM
5	(Tan et al., 2011)	U	Y	Y	Y	N	N	Y	Y	-		MEDIUM
6	(Kyle et al., 2013)	U	Y	Y	Y	N	N	Y	Y	-		MEDIUM
7	(Mao et al., 2024)	U	Y	Y	Y	N	N	Y	Y	-		MEDIUM

Y: yes; U: unclear; N: no; NA: not applicable.
JBI CRITICAL APPRAISAL CHECKLIST FOR CASE-CONTROL
Q1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? Q2. Were cases and controls matched appropriately? Q3. Were the same criteria used for identification of cases and controls? Q4. Was exposure measured in a standard, valid and reliable way? Q5. Was exposure measured in the same way for cases and controls? Q6. Were confounding factors identified? Q7. Were strategies to deal with confounding factors stated? Q8. Were outcomes assessed in a standard, valid and reliable way for cases and controls? Q9. Was the exposure period of interest long enough to be meaningful? Q10. Was appropriate statistical analysis used?
JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES Q1. Were the criteria for inclusion in the sample clearly defined? Q2. Were the study subjects and the setting described in detail? Q3. Was the exposure measured in a valid and reliable way? Q4. Were objective, standard criteria used for the measurement of the condition? Q5. Were confounding factors identified? Q6. Were strategies to deal with confounding factors stated? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was appropriate statistical analysis used?

Table 3
Up- and downregulated markers in high capsular contracture

Upregulated marker in high CC	Downregulated marker in high CC
TIMP 1	TIMP4
TIMP 2	ACAN
CysLTR2	COL3A1
TNF-alpha	TSG-6
IL8	HA
MMP12	IL10
MMP2	CysLTR1
	PRKAR2B

CC, capsular contracture

myositis (MASI) compared to women with myositis without implants (IIM) (81.8% vs. 31.6%; OR 9.8, 95% CI 1.77–96.79). A decrease in the HLA-DRB10301 (9.1% vs. 55.3%; OR 0.1, 95% CI 0.002–0.63) and HLA-DQA1*0501 (18.2% vs. 57.9%; OR 0.2, 95% CI 0.02–0.87) variants was also observed.[12]

Accordingly, the researchers compared the MASI group with a group of women with implants but without myositis (SIC), and found a higher frequency of the HLA-DQA10102 allele in MASI vs. SIC (42.3% vs. 23.1%). A further combined analysis showed higher frequency of HLA-DQA10102 in MASI vs. IIM and SIC. Furthermore, the MASI patients had lower levels of DRB10301, DQA10501, and DRB1 EYSTS variants. This study highlighted the importance of considering the interaction between genetic and environmental factors in autoimmune diseases. A limitation was the small sample size and lack of control over the confounding factors.[12]

Genetic variants and capsular contracture

Six cross-sectional studies were included that involved a total of 137 patients with a mean age ranging from 27 to 52.5 years. Five of the studies compared genetic variants with Baker grades of capsular contracture, whereas only 1 considered the implant texture (Table 1).

The studies identified various types of markers. Different pro- and anti-inflammatory receptors were associated with severe capsular contracture (Baker grades III and IV), including a significant increase in cysLTR2, TNF-α, and IL-8, with no changes in IL-10 or cysLTR1 expression. The expression of other markers, such as COL3A1, decreased as the severity of capsular contracture increased.

In addition, 2 studies analyzed the enzymatic variants of extracellular matrix-degrading proteinases, MMP-2 and MMP-12, along with their tissue inhibitors, TIMP-1, TIMP-2, and TIMP-4. The findings revealed higher expression of MMP-2, MMP-12, TIMP-1, and TIMP-2 in capsules from patients with textured implants and capsular contracture grades II, III, and IV. Conversely, markers such as TIMP-4 and aggrecan, a proteoglycan involved in extracellular matrix composition (ACAN)[31] showed decreased expression in higher contracture grades. Other components of the extracellular matrix, such as hyaluronan (HA) and TSG-6, were also assessed, revealing a significant negative correlation between capsular contracture severity and their expression levels.

Finally, in an effort to understand the etiology of the periprosthetic capsule, a study assessed PRKAR2B as a potential diagnostic gene. This gene is associated with M1 macrophages and follicular helper T cells, with its expression decreasing in lower contracture grades. Additionally, several signaling pathways were identified, including cGMP-PKG, PI3K-Akt, human papillomavirus infection, AMPK, and thyroid hormone pathways. Table 3 provides an overview of the upregulated and downregulated genes in severe capsular contracture.

Discussion

Despite technological and safety advancements in the breast implant industry, local and systemic complications continue to be reported today. Understanding genetic predisposition to autoimmune responses and capsular contracture is crucial for clinical decision-making. The identification of genetic markers can help to identify the patients who are at high risk. Additionally, targeted therapies that

address specific inflammatory or fibrotic pathways could be developed to mitigate the risk of severe complications in genetically predisposed individuals. The markers found are involved in the regulation of inflammation, immune response, and extracellular matrix remodeling—processes crucial for maintaining tissue homeostasis and responding to various pathologies.

Genetic variants and autoimmunity

As Shoenfeld and Agmon–Levin described autoimmune/inflammatory syndrome induced by adjuvants (ASIA), there has been an intense search for a causal relationship between silicone and the immune response, establishing a possible link with autoimmune symptoms. However, this association is not yet widely accepted or definitive.[13,14]

In our search, only one study showed a significant prevalence of the HLA-DQ10102 allele in Caucasian women with myositis and breast implants compared to those with myositis without implants or healthy women with breast implants.[12] These results are consistent with those of previous studies indicating that patients with breast implants and HLA-DRB1, HLA-DR53 and HLA-DQ alleles are more susceptible to developing autoimmune diseases.[15,16] The interaction between genetic predisposition and immune response plays a critical role in the development of autoimmune complications. Genetic variants in HLA alleles may contribute to aberrant immune activation upon exposure to silica, thereby leading to a heightened inflammatory state. HLA markers have been implicated in autoimmune complications associated with breast implants, but definitive conclusions remain elusive owing to several methodological challenges. Small sample sizes limit statistical power, while population biases, predominantly in Caucasian women, reduce generalizability to diverse genetic backgrounds.[12,15,16] Therefore, longitudinal studies monitoring HLA markers in women with breast implants are needed to determine whether genetic predisposition plays a significant role in the onset of autoimmune diseases in this population.

Genetic variants and capsular contracture

Local complications, such as capsular contracture, have incompletely understood pathophysiology, and a multifactorial etiology is suggested.[6] It is known to form a provisional extracellular matrix of proteins including fibronectin, fibrinogen, and albumin.[17] Initially, there is infiltration of neutrophils that secrete pro-inflammatory cytokines, and mast cell degranulation leads to the recruitment of monocytes and differentiated macrophages.[8,18] After 2 or 3 weeks, M1 macrophages persist, recruited by TNF-β, PDGF, PF4, MCP-1,2,3,4, and MIP-1α and MIP-1β. Fibroblasts, attracted by growth factors, differentiate into myofibroblasts and contribute to the development of capsular contracture.[17] This inflammatory response may be influenced by individual genetic variants, it has been shown that homozygous G/G TGF-β1 polymorphisms are commonly associated with fibroproliferative illnesses, a pilot study identified a homozygous TGF-β1 polymorphism (codon 25; genotype Arg25Arg) in nearly all patients with CC, suggesting a potential genetic predisposition.[19]

Several additional factors contribute to the development of capsular contracture. The presence of bacterial biofilm is hypothesized to induce a chronic inflammatory response that triggers persistent immune activation and fibrotic remodeling. This prolonged inflammation may contribute to fibroblast activation and extracellular matrix deposition, exacerbating the severity of capsular contracture, as clinical trials and animal studies have found high percentages of microorganisms in high Baker grade capsules (III and IV).[20–22] Other factors influencing the development of capsular contracture include implant texture, with smooth implants having higher rates of capsular contracture compared to textured implants (OR = 2.80, P < 0.00001 [95% CI, 1.92 – 4.08]), and implant placement, where subpectoral placement is associated with lower rates of capsular contracture compared to prepectoral (subglandular) placement (OR = 0.35, P < 0.00001 [95% CI, 0.25 – 0.50]).[23] Although biofilm, texture, and implant placement are considered as strong contributors to capsular contracture development, no evidence currently links specific genetic variants to differential responses between these factors.

Additional factors which may contribute to capsular contracture are hematoma and silicone implant leakage.[8] A recent transcriptomic study identified marked similarities in gene expression patterns between the immune response associated with capsular contracture and allograft rejection,[24]

reinforcing that immune-mediated mechanisms may play a central role in capsular contracture development.

There are also differences between capsular contracture following implant-based breast reconstruction and cosmetic breast augmentation. Beyond the risk associated with implant texture, surgical technique, and pre-existing immune factors, additional elements also increase the risk of capsular contracture development in reconstructive breast augmentation. The history of breast cancer and associated oncologic treatments influence the immune responses to implants, potentially altering the local cytokine profiles and immune cell infiltration patterns. This may create a pro-inflammatory microenvironment that predisposes patients to fibrosis and contracture.[25] Surgical site infection is a common cause of capsular contracture in reconstructive surgery, particularly in patients undergoing mastectomy and immediate implant placement. Furthermore, adjuvant therapy appears to significantly increase the risk of fibrosis and contracture affecting the Wnt (Wingless) pathway and promoting fibroproliferation.[26,27] Although our results have been heterogeneous, the genetic markers analyzed in the studies share a common involvement in processes of inflammation, cellular remodeling, and immune response.

Inflammation markers and immune response

TNF-α, IL8, and IL10 are cytokines that are part of the foreign body inflammatory response.[17] The expression of these cytokines was observed in the analyzed studies, where the pro-inflammatory cytokines TNF-α and IL8 were found to be more highly expressed in contracted capsules, while other anti-inflammatory cytokines such as IL10 did not show increased expression in contracted capsules compared to the controls.[28–30] The increased expression of TNF-α and IL8, along with the decreased expression of IL10 in contracted capsules, was also observed *in vitro*.[31] These findings highlight the importance of these markers in the inflammatory process that occurs during the development of capsular contracture.

In our analysis, other inflammatory markers, such as cysteinyl leukotrienes 2 (cysLTR2), were found, which were highly expressed in contracted capsules.[28] The expression of cysLTR2 has been associated with fibroblast proliferation and collagen deposition, in addition to being linked to angiogenesis in tumors in mice.[32,33] Further studies with larger sample size are needed to corroborate the important roles that these mediators may play in capsular contracture.

Extracellular matrix remodeling

Among the important factors that lead to the development of fibrosis are MMPs and TIMPs, whose dysregulation can lead to various fibrosis-associated diseases.[34,35] Our results highlight the expression of genes that code for MMPs and TIMPs in severe contracture capsules.[36] MMP12 may have a profibrotic role in pulmonary fibrosis, being implicated in collagen production and fibroblast activity.[37,38] Similarly, the accumulation of TIMP1 and TIMP2 has been shown to be a factor in fibrosis during hepatic fibrogenesis.[39]

A recent transcriptomic study showed a significant downregulation of TIMP4 in breast with III and IV capsular contracture and upregulation of MMP1, MMP7, MMP8, MMP11, and MMP12, which is consistent with our findings. More interestingly, it revealed a strong correlation between B cell activation and capsular contracture, and highlighted the gene pathways that are most significantly upregulated in capsular contracture which included graft-versus-host disease, autoimmune thyroid disease, and allograft rejection, suggesting an immune-mediated rejection of the breast implant, analogous to allograft rejection.[24] This supports the hypothesis that capsular contracture may not be solely a fibrotic process but rather an immune-mediated response to foreign material.

In the reviewed studies, some markers such as TSG-6, HA, and ACAN were also found to be expressed in fewer contracted capsules, highlighting the importance of these proteins in the cellular remodeling process following implantation.[30] The decrease in these markers with the progression of capsular contracture may indicate the activation of other pathways that interfere with this remodeling.[40] A longitudinal in vivo study of these markers could provide valuable insights into the role of these pathways in capsular contracture progression. Other reported markers include PRKAR2B, which showed low expression in severe capsular contracture and is therefore reported as a prognostic

marker.[41] The identification of genes with prognostic value could be a valuable strategy for preventing capsular contracture.

This systematic review had some limitations related to the information gathered. Specifically, in the context of exploring potential autoimmune links between genetics and breast implants, the inclusion of certain case reports could provide additional insights. However, the absence of statistical validation in case reports could introduce bias regarding the genetic markers identified. Although adding *in vitro* or *in vivo* studies could enrich the review, it would also increase the heterogeneity of the findings.

In general, the included studies had small sample sizes. Additionally, most of them did not consider other confounding factors, such as implant texture, which affects molecular expression and histological composition[42–44] and therefore may influence the development of capsular contracture. The cross-sectional nature of most of the studies prevented temporal tracking of changes in gene expression.

Finally, the heterogeneity of the study methodologies was also a major limitation, preventing the performance of meta-analyses that could have facilitated provision of robust conclusions about the markers expressed during the development of capsular contracture. Future research that use uniform methodologies, with standardized patient selection criteria, genetic analysis techniques, and outcome measures to improve comparability across studies will help to perform meta-analyses, which may clarify the role of genetic predisposition in CC.

Despite these limitations, the identification of genes that may contribute to the development of autoimmune complications and capsular contracture in women with breast implants is of vital importance for understanding the relationship between implants and the reported complications. It is essential to deepen the study of molecules that may help elucidate the etiopathogenesis of capsular contracture and development of autoimmune diseases in some women with implants. The typification of HLA markers and constant monitoring of disease development in these patients could have significant clinical and epidemiological relevance, as well as allow for a deeper genetic analysis to determine the prognostic and therapeutic behavior of these complications. Further approaches in omics sciences could provide valuable insights into the progression of capsular contracture and help identify potential treatment strategies. Transcriptomic approaches, such as single-cell RNA sequencing (scRNA-seq), could offer a more precise characterization of the immune response by distinguishing between different immune cell populations involved in capsular contracture, revealing specific inflammatory or fibrotic pathways that contribute to capsular contracture at a cellular level. Metagenomic sequencing could also help to identify bacterial species associated with biofilm formation on implants, clarifying their role in triggering chronic inflammation and fibrosis. These advanced techniques could enhance our understanding of the underlying mechanisms driving capsular contracture and aid in the development of targeted therapeutic interventions.

Conclusions

Most associations found in the studies were between genetic markers and capsular contracture, with most of these markers being indicators of inflammation. Although no evidence currently links specific genetic variants to responses associated with implant texture, placement, or biofilm formation, transcriptomic and metagenomic studies suggest that immune-mediated mechanisms play a central role in capsular contracture development.

Our findings underscore the importance of further research into genetic predisposition and immune responses in patients undergoing breast implantation. The identification of genetic and molecular markers associated with capsular contracture could enhance our understanding of this condition and allow personalized risk assessment that facilitates clinical decision-making. Future studies integrating multi-omics approaches, such as single-cell RNA sequencing and microbiome profiling, could provide deeper insights into these processes and refine clinical management strategies.

Competing Interests

The authors declare that they have no conflicts of interest related to this work.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. No Ethics Committee approval was needed.

Author Contributions

Alan González: Conceptualization, Supervision, Project administration, Reviewing and Editing. **Daniela Quibano-Ordoñez:** Investigation, Validation, Writing - Original Draft, Writing - Review & Editing, Visualization **Laura Ortega-Muñoz:** Methodology, Investigation, Validation, Writing - Original Draft, Writing - Review & Editing. **Patricia E. Vélez-Varela:** Reviewing and Editing, Supervision. **Pedro A. Moreno:** Reviewing and Editing, Supervision.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4.0 in order to review redaction of writing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Kaoutzanis C, Winocour J, Unger J, Gabriel A, Maxwell GP. The evolution of breast implants. *Semin Plast Surg*. 2019;33(4):217–223. doi:10.1055/s-0039-1696985.
2. ISAPS. Global Statistics. 2022. https://www.isaps.org/discover/about-isaps/global-statistics/. [Accessed April 29, 2024].
3. Sieber DA, Adams WP. What's your micromort? A patient-oriented analysis of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). *Aesthet Surg Jl*. 2017;37(8):887–891. doi:10.1093/asj/sjx127.
4. Watad A, Rosenberg V, Tiosano S, et al. Silicone breast implants and the risk of autoimmune/rheumatic disorders: A real-world analysis. *Int J Epidemiol*. 2018;47(6):1846–1854. doi:10.1093/ije/dyy217.
5. Borba V, Malkova A, Basantsova N, et al. Classical examples of the concept of the ASIA syndrome. *Biomolecules*. 2020;10(10):1436. doi:10.3390/biom10101436.
6. Lieffering AS, Hommes JE, Ramerman L, et al. Prevalence of local postoperative complications and breast implant illness in women with breast implants. *JAMA Netw Open*. 2022;5(10):e2236519. doi:10.1001/jamanetworkopen.2022.36519.
7. De Bakker E, Van Den Broek LJ, Ritt MJPF, Gibbs S, Niessen FB. The histological composition of capsular contracture focussed on the inner layer of the capsule: An Intra-Donor Baker-I Versus Baker-IV comparison. *Aesth Plast Surg*. 2018;42(6):1485–1491. doi:10.1007/s00266-018-1211-1.
8. Gorgy A, Barone N, Nepon H, et al. Implant-based breast surgery and capsular formation: When, how and why?—A narrative review. *Ann Transl Med*. 2023;11(11):385. doi:10.21037/atm-23-131.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021:n71 Published online March 29. doi:10.1136/bmj.n71.
10. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: Pitfalls and hints. *Heart Lung Vessel*. 2013;5(4):219–225.
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—A web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. doi:10.1186/s13643-016-0384-4.
12. O'Hanlon T, Koneru B, Bayat E, et al. Immunogenetic differences between Caucasian women with and those without silicone implants in whom myositis develops. *Arthritis Rheum*. 2004;50(11):3646–3650. doi:10.1002/art.20587.
13. Shoenfeld Y, Agmon-Levin N. ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmunity*. 2011;36(1):4–8. doi:10.1016/j.jaut.2010.07.003.
14. Caravantes-Cortes MI, Roldan-Valadez E, Zwojewski-Martinez RD, Salazar-Ruiz SY, Carballo-Zarate AA. Breast prosthesis syndrome: Pathophysiology and management algorithm. *Aesth Plast Surg*. 2020;44(5):1423–1437. doi:10.1007/s00266-020-01663-9.
15. Meier LG, Barthel HR, Seidl C. Development of polyarthritis after insertion of silicone breast implants followed by remission after implant removal in 2 HLA-identical sisters bearing rheumatoid arthritis susceptibility genes. *J Rheumatol*. 1997;24(9):1838–1841.
16. Young VL, Nemecek JR, Schwartz BD, Phelan DL, Schorr MW. HLA typing in women with breast implants. *Plast Reconstr Surg*. 1995;96(7):1497.
17. Klopfleisch R, Jung F. The pathology of the foreign body reaction against biomaterials. *J Biomedical Materials Res*. 2017;105(3):927–940. doi:10.1002/jbm.a.35958.
18. Faruq O, Chien PN, Dönmez N, Nam SY, Heo CY. Functionalization of silicone surface with drugs and polymers for regulation of capsular contracture. *Polymers (Basel)*. 2021;13(16):2731. doi:10.3390/polym13162731.

19. Veras-Castillo ER, Cardenas-Camarena L, Lyra-Gonzalez I, et al. Controlled clinical trial with pirfenidone in the treatment of breast capsular contracture: Association of TGF-β polymorphisms. *Ann Plast Surg*. 2013;70(1):16–22. doi:10.1097/SAP.0b013e31822284f4.
20. Ajdic D, Zoghbi Y, Gerth D, Panthaki ZJ, Thaller S. The relationship of bacterial biofilms and capsular contracture in breast implants. *Aesthet Surg J*. 2016;36(3):297–309. doi:10.1093/asj/sjv177.
21. Pajkos A, Deva AK, Vickery K, Cope C, Chang L, Cossart YE. Detection of subclinical infection in significant breast implant capsules. *Plast Reconstr Surg*. 2003;111(5):1605–1611. doi:10.1097/01.PRS.0000054768.14922.44.
22. Tamboto H, Vickery K, Deva AK. Subclinical (Biofilm) infection causes capsular contracture in a porcine model following augmentation mammaplasty. *Plast Reconstr Surg*. 2010;126(3):835–842. doi:10.1097/PRS.0b013e3181e3b456.
23. Haas E, Christodoulou N, Secanho M, et al. Capsular contracture after breast augmentation: A systematic review and meta-analysis. *Aesthet Surg J Open Forum*. 2025;7:ojaf003. doi:10.1093/asjof/ojaf003.
24. Larsen A, Fritz BG, Weltz TK, et al. Transcriptome of capsular contracture around breast implants mimics allograft rejection: A matched case-control study. *Plast Reconstr Surg*. 2024 Published online December 24. doi:10.1097/PRS.0000000000011938.
25. Marconi R, Serafini A, Giovanetti A, et al. Cytokine modulation in breast cancer patients undergoing radiotherapy: A revision of the most recent studies. *IJMS*. 2019;20(2):382. doi:10.3390/ijms20020382.
26. Lipa JE, Qiu W, Huang N, Alman BA, Pang CY. Pathogenesis of radiation-induced capsular contracture in tissue expander and implant breast reconstruction. *Plast Reconstr Surg*. 2010;125(2):437–445. doi:10.1097/PRS.0b013e3181c82d05.
27. Luvsannyam E, Patel D, Hassan Z, Nukala S, Somagutta MR, Hamid P. Overview of risk factors and prevention of capsular contracture following implant-based breast reconstruction and cosmetic surgery: A systematic review. *Cureus*. 2020 Published online September 9. doi:10.7759/cureus.10341.
28. D'Andrea F, Nicoletti GF, Grella E, et al. Modification of cysteinyl leukotriene receptor expression in capsular contracture: preliminary results. *Ann Plast Surg*. 2007;58(2):212–214. doi:10.1097/01.sap.0000237680.59808.86.
29. Tan KT, Wijeratne D, Shih B, Baildam AD, Bayat A. Tumour necrosis factor-α expression is associated with increased severity of periprosthetic breast capsular contracture. *Eur Surg Res*. 2010;45(3-4):327–332. doi:10.1159/000321009.
30. Tan KT, Baildam AD, Juma A, Milner CM, Day AJ, Bayat A. Hyaluronan, TSG-6, and inter-α-inhibitor in periprosthetic breast capsules: Reduced levels of free hyaluronan and TSG-6 expression in contracted capsules. *Aesthet Surg J*. 2011;31(1):47–55. doi:10.1177/1090820X10391778.
31. Kyle DJT, Harvey AG, Shih B, Tan KT, Chaudhry IH, Bayat A. Identification of molecular phenotypic descriptors of breast capsular contracture formation using informatics analysis of the whole genome transcriptome. *Wound Repair Regen*. 2013;21(5):762–769. doi:10.1111/wrr.12077.
32. Oyoshi MK, He R, Kanaoka Y, et al. Eosinophil-derived leukotriene C4 signals via type 2 cysteinyl leukotriene receptor to promote skin fibrosis in a mouse model of atopic dermatitis. *Proc Natl Acad Sci U S A*. 2012;109(13):4992–4997. doi:10.1073/pnas.1203127109.
33. Duah E, Teegala LR, Kondeti V, et al. Cysteinyl leukotriene 2 receptor promotes endothelial permeability, tumor angiogenesis, and metastasis. *Proc Natl Acad Sci USA*. 2019;116(1):199–204. doi:10.1073/pnas.1817325115.
34. Kremastiotis G, Handa I, Jackson C, George S, Johnson J. Disparate effects of MMP and TIMP modulation on coronary atherosclerosis and associated myocardial fibrosis. *Sci Rep*. 2021;11(1):23081. doi:10.1038/s41598-021-02508-4.
35. Shan L, Wang F, Zhai D, Meng X, Liu J, Lv X. Matrix metalloproteinases induce extracellular matrix degradation through various pathways to alleviate hepatic fibrosis. *Biomed Pharmacother*. 2023;161:114472. doi:10.1016/j.biopha.2023.114472.
36. Ulrich D, Ulrich F, Pallua N, Eisenmann-Klein M. Effect of tissue inhibitors of metalloproteinases and matrix metalloproteinases on capsular formation around smooth and textured silicone gel implants. *Aesth Plast Surg*. 2009;33(4):555–562. doi:10.1007/s00266-009-9335-y.
37. Giannandrea M, Parks WC. Diverse functions of matrix metalloproteinases during fibrosis. *Dis Models Mech*. 2014;7(2):193–203. doi:10.1242/dmm.012062.
38. Madala SK, Pesce JT, Ramalingam TR, et al. Matrix metalloproteinase 12-deficiency augments extracellular matrix degrading metalloproteinases and attenuates il-13–dependent fibrosis. *J Immunol*. 2010;184(7):3955–3963. doi:10.4049/jimmunol.0903008.
39. Hu Y, Li D, Lu H. Modified synthetic siRNA targeting tissue inhibitor of metalloproteinase-2 inhibits hepatic fibrogenesis in rats. *J Gene Med*. 2007;9(3):217–229. doi:10.1002/jgm.1009.
40. Ma L, Hua L, Yu W, Ke L, Li L. TSG-6 inhibits hypertrophic scar fibroblast proliferation by regulating IRE1α/TRAF2/NF-κB signalling. *Int Wound J*. 2022;20(4):1008–1019. doi:10.1111/iwj.13950.
41. Mao Y, Hou X, Fu S, Luan J. Transcriptomic and machine learning analyses identify hub genes of metabolism and host immune response that are associated with the progression of breast capsular contracture. *Genes Dis*. 2024;11(3):101087. doi:10.1016/j.gendis.2023.101087.
42. Daneshgaran G, Gardner DJ, Chen HHA, et al. Silicone breast implant surface texture impacts gene expression in periprosthetic fibrous capsules. *Plast Reconstr Surg*. 2023;151(1):85–95. doi:10.1097/PRS.0000000000009800.
43. Fischer S, Hirche C, Reichenberger MA, et al. Silicone implants with smooth surfaces induce thinner but denser fibrotic capsules compared to those with textured surfaces in a rodent model. *PLoS ONE*. 2015;10(7):e0132131. doi:10.1371/journal.pone.0132131.
44. Wells HJ, Yang JCC, Edelstein-Keshet L, Isaac KV. Implant texture and capsular contracture: A review of cellular and molecular pathways. *Plast Reconstr Surg - Global Open*. 2024;12(5):e5802. doi:10.1097/GOX.0000000000005802.