Segmental vitiligo: A distinct entity with unique pathogenesis and clinical implications

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Segmental vitiligo (SV) is characterized by unilateral depigmentation, frequent leukotrichia, early stabilization, and unique pathomechanisms that differentiate it from nonsegmental vitiligo. This review systematically examines the epidemiology, clinical features, diagnosis, pathogenesis, and therapeutic advances in SV, emphasizing its classification as a distinct disease entity. Emerging evidence has provided significant insights into SV pathogenesis, including neurovascular factors, immune dysregulation, oxidative stress, and melanocyte dysfunction. Clinically, SV requires differentiation from other hypopigmentation disorders owing to its distinct progression and therapeutic challenges. Although conventional therapies exhibit limited efficacy, emerging approaches such as cellular grafting and targeted immunomodulation hold promise. This review advocates for future research to focus on the integration of multiomics data to establish SV-specific biomarkers and personalized diagnostic and therapeutic strategies.

Keywords: Immune dysregulation, Mosaicism, Neurogenic theory, Precision therapy, Segmental vitiligo

INTRODUCTION

Vitiligo, an acquired depigmenting disorder characterized by melanocyte loss, manifests as depigmented macules affecting the skin, hair, or both. Global epidemiological studies estimate its prevalence at 0.5−1%, although some degree of regional variation exists (Behl and Bhatia, 1972; Ezzedine et al, 2012b). Approximately 50% of cases present before the age of 20 years (Taïeb and Picardo, 2009).

Current international consensus classifies the condition into 3 forms: nonsegmental vitiligo (NSV), segmental vitiligo (SV), and undetermined/unclassified vitiligo (van Geel et al, 2023). Although NSV typically exhibits symmetrical/generalized depigmentation and is associated with systemic autoimmunity and progressive course, SV is characterized by unilateral distribution, frequent early stabilization, and prominent follicular involvement (leukotrichia). Accumulating evidence underscores its classification as a distinct disease from NSV with differing epidemiology, clinical features, pathogenesis, and therapeutic responses. Epidemiological studies indicate that SV accounts for 5−27.9% of vitiligo cases (van Geel and Speeckaert, 2017), with a segmental-to-nonsegmental ratio of approximately 1:4.6 in childhood (Farajzadeh et al, 2023). A recent large-scale analysis (n = 925) highlights a younger mean age of onset (20.73 years) and predilection for facial (49.3%) and truncal (33.8%) regions (Ma et al, 2021). In addition, SV demonstrates clinical trajectories challenging traditional views of inherent stability, including higher leukotrichia prevalence (45.2%) and lower recurrence rate (reported rates ranging from 11.9 to 21.1%), particularly in facial subtypes (Oh et al, 2021; Xu et al, 2022b). Notably, recurrence typically occurs within the same anatomical area as the initial lesion, aligning with somatic mosaicism hypothesis (Oh et al, 2021).

Recent advances have also reshaped our understanding of SV pathogenesis, emphasizing somatic mosaicism, neurogenic factors (eg, sympathetic dysfunction) (Fu et al, 2025), anatomical correlation with arterial perfusion territories (Benzekri et al, 2024), and local immune microenvironment alterations driven by exosomal microRNA (miRNA) regulation and localized autoimmunity (Li et al, 2022; Speeckaert et al, 2020). In addition, oxidative stress and melanocyte dysfunction may also play an important role in SV.

Clinically, progress has been made in identifying progressive SV and differentiating it from other segmental hypopigmentation disorders (El-Taweel et al, 2021; Roh et al, 2019). Therapeutic management of SV mainly includes topical agents, phototherapy, surgical intervention, and the combination of these therapies. However, SV exhibits

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Abbreviations: BSA, body surface area; cDC1, type 1 conventional dendritic cell; CGRP, calcitonin gene-related peptide; COMT, catechol-O-methyltransferase; H_2O_2, hydrogen peroxide; iHSP70, inducible HSP70; IRF, IFN regulatory factor; McSC, melanocyte stem cell; miRNA, microRNA; MKTP, melanocyte-keratinocyte transplantation procedure; MMP9, matrix metalloproteinase 9; MV, mixed vitiligo; NB-UVB, narrowband UVB; NCST, noncultured suspension transplantation; ND, nevus depigmentosus; NE, norepinephrine; NNT, nicotinamide nucleotide transhydrogenase; NPY, neuropeptide Y; NSV, nonsegmental vitiligo; RCM, reflectance confocal microscopy; RCT, randomized controlled trial; redox, reduction−oxidation; SND, segmental nevus depigmentosus; SOD, superoxide dismutase; SV, segmental vitiligo; Th, T helper; Treg, regulatory T cell

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suboptimal therapeutic responses to conventional interventions, including topical corticosteroids and phototherapy, with significant repigmentation achieved in merely about 7.3% of cases (Xu et al, 2022a). Emerging therapeutic approaches, including Jak inhibitors, autologous melanocyte transplantation, and combination therapies (Khalili et al, 2022; Olamiju and Craiglow, 2020; Souroujon et al, 2023), demonstrate promise but require further clinical validation and improvement. Therefore, this review synthesizes contemporary insights of SV epidemiology, pathogenesis, and clinical practice, advocating for its recognition as a distinct entity, and calls for a precision medicine paradigm in SV care. Critically, future research is supposed to integrate multiomics data to unravel SV-specific genetic, epigenetic, and neuroimmune interplay, so as to identify biomarkers and advance targeted therapies for precision-based diagnosis and treatment.

CLINICAL FEATURES AND DIAGNOSIS

SV, characterized by unilateral, dermatomal depigmentation, presents a distinct entity from NSV. Representative clinical photographs illustrating the characteristic features of SV are shown in Figure 1. Epidemiological studies across diverse populations reflect the patterns of SV regarding prevalence, age at onset, sex ratio, and associated symptoms.

Epidemiology

In the United States, clinician-diagnosed SV prevalence ranges from 0.09 to 0.12% (self-reported: 0.61%) (Gandhi et al, 2022). Globally, childhood SV demonstrates a female predominance (female-to-male ratio of 1.3:1) and a nonsegmental-to-segmental ratio of 4.6:1, with the highest and lowest ratios observed in Africa (11.56) and the United States (3.02), respectively (Farajzadeh et al, 2023). These geographical variations may reflect the potential influences of genetic and environmental factors, although selection bias and reporting differences are likely more significant contributors to these observations.

Age of onset

SV manifests earlier. The average age of onset for SV is about 16−21 years, which is 8−10 years earlier than that of NSV (Hann and Lee, 1996; Ma et al, 2021; Silva de Castro et al, 2012). A Chinese Han cohort (n = 925) showed a peak incidence during adolescence (10−20 years: 38.8%) (Ma et al, 2021). In this cohort, early-onset SV (≤17 years) exhibited longer disease duration and better treatment-induced repigmentation than late-onset cases (>17 years) (Ma et al, 2021).

Lesion characteristics

Clinically, SV is a distinct subtype of vitiligo characterized by unilateral, dermatomal depigmentation that typically follows the distribution of cutaneous dermatomes or Blaschko's lines (Ezzedine et al, 2012b). It manifests as rapidly progressive, asymmetric macules/patches confined to 1 side of the body, typically followed by long-term stability within 1−2 years after onset (van Geel and Speeckaert, 2017). Unlike NSV, SV shows early onset (frequently in childhood), less association with autoimmune comorbidities, and frequent leukotrichia. SV predominantly affects the head, trunk, and neck regions, with studies reporting prevalence rates of 49.3, 33.8, and 29.4%, respectively. Another study indicated that head/neck involvement occurs in 66.7% of childhood vitiligo cases (Farajzadeh et al, 2023; Ma et al, 2021). Facial and truncal SV exhibits distinct anatomical patterns, classified into 10 subtypes (5 facial, 5 truncal) on the basis of distribution and spread dynamics (Oh et al, 2021). Common facial subtypes include chin-mandible (F5-CM: 19.4%) and central face (F3-CF: 18.3%), whereas truncal subtypes frequently involve the pubic region and legs (T5-PL: 7.2%) or upper trunk (T3-UT: 7.4%) (Oh et al, 2021). This classification aids in predicting lesion spread and recurrence patterns. On the other hand, SV is also marked by a smaller affected body surface area (BSA), similar to mild-to-moderate NSV (affected BSA ≤10%): SV, 2.91 ± 2.39%; mild-to-moderate NSV, 3.41 ± 1.96%; severe NSV (affected BSA >10%), 22.74 ± 13.96% (Xu et al, 2022b).

Associated features

As for the accompanying symptoms, SV lesions exhibit more frequent leukotrichia (SV: 45.2%; mild-to-moderate NSV: 8.5%; severe NSV: 28.2%) (Xu et al, 2022b) and lower rates of halo nevi (10.2% in SV vs 45.8% in NSV) and autoimmune comorbidities (eg, antithyroid antibodies in 1.7% of SV vs 29.6% of NSV) than NSV (Ezzedine et al, 2011), reflecting its localized pathology. European studies confirm SV's early stabilization, reflected in less disease activity signs than NSV (hypochromic areas/borders: 8.8 vs 32.9%; confetti-like depigmentation: 1.8 vs 28.6%; Koebner phenomenon: 8.5 vs 38.0%) (Delbaere et al, 2024; Ezzedine et al, 2011).

Disease course

The disease course of SV typically involves rapid progression followed by stabilization within 1−2 years. When SV was stable for at least 2 years, the likelihood of reactivation was 5 times less than SV with stability <2 years ($P = .16$); in NSV, duration of stability showed no association with reactivation risk, prone to reactivation even after prolonged stability (Taneja et al, 2022). As for recurrence, SV exhibits a significantly lower recurrence rate than NSV, the latter of which demonstrates a recurrence rate as high as 40% within 6 months (Cavalié et al, 2015). Bae et al showed that SV recurrence occurs in 11.9% of cases after a median latency of 4.1 years, and Xu et al reported an SV recurrence rate of 21.1% (Oh et al, 2021; Xu et al, 2022b). Facial SV demonstrates higher recurrence risk than truncal SV (15.2 vs 6.1%), with most recurrences (92.7%) confined to the same anatomical subtype as initial lesions (eg, F5-CM lesions recurring within the chin-mandible region), implying a postzygotic pathogenesis for SV, potentially mediated by somatic sequence variants or epigenetic events (Oh et al, 2021). Although leukotrichia-associated melanocyte depletion often limits repigmentation efficacy, early-onset SV shows better treatment response (31.2 repigmentation vs 20.9% in later onset), likely owing to shorter disease duration and preserved melanocyte reservoirs (Ma et al, 2021).

Thus, more refined clinical features of SV (including disease extent, onset time, and anatomical subtype) could guide treatment decisions and prognosis better.

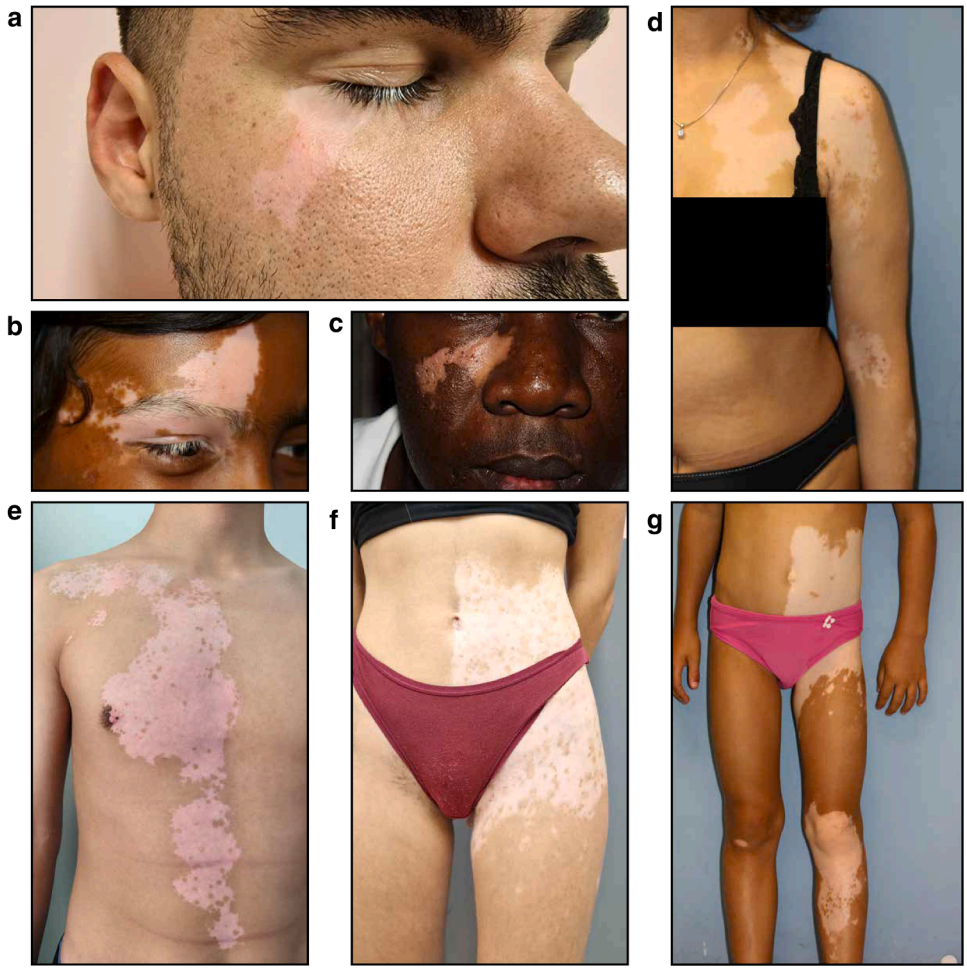

Figure 1. Representative clinical presentations of SV. (**a**–**c**) SV involving the face: (**a**) Right periorbital lesion with poliosis of the eyelashes, (**b**) right periocular and frontal lesion with poliosis of the eyelashes and eyebrows, and (**c**) right cheek lesion. (**d**) SV on the left shoulder and anterior chest in a female patient. (**e**) SV involving the right shoulder, anterior chest, and abdomen in a male patient. (**f**) SV on the left abdomen, hip, and anterior thigh in a female patient. (**g**) Mixed vitiligo in a male patient, showing coexistence of SV on the left abdomen, hip, anterior thigh, and anterior lower leg and NSV on bilateral knees. Written informed consent was obtained from all individual participants (or their parents/guardians) for the publication of their identifiable images. SV, segmental vitiligo; NSV, nonsegmental vitiligo.

Diagnostic criteria and challenges

Accurate diagnosis of SV is paramount owing to its distinct prognostic and therapeutic implications compared with NSV and has evolved with validated clinical criteria and emerging biomarkers.

No internationally unified gold standard or specific biomarkers or laboratory tests exist for SV. SV diagnosis currently relies on expert consensus and clinical experience. According to the 2023 recommendation of the International Vitiligo Task Force, the diagnostic core of SV is unilateral segmental depigmented macules, combined with a rapid stabilization course (no progression for ≥12 months) and ancillary investigations (eg, Wood's lamp) to exclude other disorders (van Geel et al, 2023). Gupta et al (2020) validated a set of diagnostic criteria for SV, comprising essential and additional features. Essential criteria include (i) unilateral depigmentation not crossing the midline, (ii) localization to a specific body area, and (iii) patterned distribution (blaschkoid, dermatomal, phylloid, checkerboard, or any other specific type) (Gupta et al, 2020; Khaitan et al, 2012). Patients should satisfy all essential criteria plus ≥1 additional criterion (eg, onset age <15 years, leukotrichia affecting >50% of lesions, or stability within 1 year) (Gupta et al, 2020; Khaitan et al, 2012). This system demonstrated high sensitivity (91.8%) and specificity (100%) against expert diagnosis and showed 93.5% agreement ($P < .001$) with expert diagnosis (Gupta et al, 2020).

Beyond clinical phenotyping, serum biomarkers now offer objective differentiation. TWEAK (TNF-like weak inducer of apoptosis) levels are significantly elevated in SV (1126.5 ± 918.25 pg/ml) versus in NSV (624.68 ± 683.07 pg/ml), with 100% sensitivity and 80.95% specificity at a cutoff of 463.5 pg/ml for distinguishing SV from NSV (El-Taweel et al, 2021). Similarly, serum levels of S100B, a marker of melanocyte damage, are positively correlated with Vitiligo Disease Activity score and Vitiligo Extent Tensity Index and are lower in stable SV (103.3 ± 23.45 pg/ml) than in active NSV (154.3 ± 39.0 pg/ml) (Shabaka et al, 2022). These biomarkers underline the differences between NSV and SV but still need further confirmation before usage in daily practice. Biomarkers such as TWEAK show promise for early SV detection but lack prospective validation in broader hypopigmentary disorders (El-Taweel et al, 2021). In addition, S100B's utility is limited to activity monitoring, not subtype differentiation (Shabaka et al, 2022).

Distinguishing SV from segmental hypopigmentary disorders, notably segmental nevus depigmentosus (SND), remains challenging owing to their identical unilateral presentations. Critical discriminators include age of onset: 96.8% of SND presents before age 10 years versus only

28.9% of SV (Roh et al, 2019). Lesion characteristics further aid differentiation: SND exhibits serrated borders (90.5% vs 41.6% in SV) and broader vertical spread (mean dermatomes: 2.71 vs 1.62) (Roh et al, 2019). In contrast, SV favors facial/trigeminal distribution (67.1% vs 12.7% in SND) with smoother margins and frequent poliosis (20.1% vs 3.2%) (Roh et al, 2019). One critical difference is the presence of the remaining melanocytes in SND, leading to a hypopigmented lesion when SV are achromic. Wood's lamp examination is key, especially in fair skin types, and reveals off-white accentuation in nevus depigmentosus (ND) versus chalk-white fluorescence in SV. Reflectance confocal microscopy (RCM) shows preserved melanocytes in ND but their loss in SV (Ezzedine et al, 2012b; Roh et al, 2019).

Several challenges complicate SV diagnosis and categorization, including ambiguous subtype classification boundaries and the absence of reliable SV biomarkers or laboratory tests. Early SV can mimic focal vitiligo (localized, unclassified until stability observed) (van Geel et al, 2023) or SND. Mixed vitiligo (MV), defined as SV with coexisting NSV lesions, further blurs subtype boundaries (Ezzedine et al, 2012b; Mulekar et al, 2006). MV progression from SV is predicted by early SV onset, >1% BSA involvement, leukotrichia, and Halo nevi (Ezzedine et al, 2012a; Kumar et al, 2022). Its management remains contentious owing to SV's recalcitrant nature versus the responsiveness of NSV to medical treatments (Ezzedine et al, 2012b; Kumar et al, 2022).

In conclusion, current diagnostic criteria for SV provide a structured framework but require integration with dynamic assessments (eg, lesion stability) and emerging biomarkers. Future efforts are supposed to prioritize noninvasive tools (eg, RCM, serum biomarkers) for prospective validation in indeterminate cases, while refining MV criteria and the subtype classification to guide targeted therapies.

INSIGHTS INTO SV MECHANISMS

Recent years have witnessed significant advances in our understanding of the pathogenesis of SV, distinguishing it further from NSV through unique and multifactorial mechanisms. This section delves into the emerging evidence supporting somatic mosaicism, neurovascular contributions, autoimmune processes, and oxidative stress as drivers of SV, offering perspectives for targeted interventions. To visually integrate these complex interactions, we have developed a comprehensive pathogenesis diagram of SV (Figure 2).

Somatic mosaicism

Recent advances have reshaped our understanding of SV pathogenesis. The somatic mosaicism hypothesis posits that SV arises from a postzygotic sequence variant occurring during embryonic development, generating a genetically distinct subpopulation of melanocytes confined to a specific body segment (Katz and Harris, 2021). This clonal population of mosaic melanocytes is hypothesized to exhibit intrinsic abnormalities, such as heightened stress susceptibility or altered immunogenicity, that render them vulnerable to localized autoimmune attack, ultimately leading to their targeted destruction and the characteristic segmental depigmentation pattern distinct from systemic autoimmune processes in NSV (Lin et al, 2025; Speeckaert et al, 2024; van Geel et al, 2013).

The striking unilateral, segmentally distributed depigmentation pattern of SV, often with sharp midline demarcation, strongly suggests an underlying somatic mosaicism. Clinical distribution studies reveal that SV lesions do not conform to classic dermatomes but instead align more closely with patterns observed in other mosaic pigmentary disorders such as segmental lentiginosis and verrucous epidermal nevus (van Geel et al, 2013). This unique "SV pattern", frequently exhibiting a V-shape on the forehead and upper trunk (observed in 46% of SV lesions in the study by van Geel et al [2013]), shares significant overlap with mosaic skin diseases and implies a developmental origin rather than a systemic autoimmune etiology (van Geel et al, 2013). Melanoblasts migrate from the neural crest along a dorsolateral pathway to colonize the fetal epidermis and hair follicles, where they differentiate into mature melanocytes (Coutant et al, 2024; van Geel et al, 2013). This trajectory predominantly covers dorsal and lateral body regions but not the midline or ventral. The unique "SV pattern" aligns with the embryologic migration route of melanoblasts, supporting the somatic mosaicism hypothesis (Speeckaert et al, 2024).

Compelling molecular evidence supports this mosaicism theory. Studies demonstrate that SV lesional skin harbors melanocytes with intrinsic abnormalities and heightened susceptibility to stress. Notably, melanocytes within SV lesions but not those from nonlesional sites of the same patient or healthy controls exhibit significantly increased expression of CXCR3B—a proapoptotic chemokine receptor implicated in melanocyte death (Passeron et al, 2022). Furthermore, stress markers such as inducible HSP70 (iHSP70), mtDNA (indicating cellular damage), and *CXCL16* mRNA (produced by stressed keratinocytes) are selectively elevated only in lesional SV skin (Passeron et al, 2022). This localized increase in stress vulnerability specifically within the affected segment implies a cell-autonomous defect confined to mosaic melanocytes.

The immune system appears to selectively target these abnormal, mosaic melanocytes. Histopathological analyses and flow cytometry consistently reveal melanocyte antigen-specific $CD8^+$ T cells at the dermal–epidermal junction in active SV lesions, exhibiting a proinflammatory phenotype characterized by high IFN-γ and TNF-α production (Shin et al, 2016; van Geel et al, 2010). This immune response, although potent locally, is generally transient and confined. Unlike NSV, SV shows no systemic alterations in regulatory T-cell (Treg) frequency or function, lacks melanocyte-specific autoantibodies, and has minimal association with systemic autoimmune diseases (Xu et al, 2022b). The inflammation typically stabilizes within 1–2 years, presumably once the susceptible mosaic melanocyte population is eliminated (Speeckaert et al, 2024).

The success of autologous melanocyte–keratinocyte transplantation in stable SV, significantly outperforming results in NSV (eg, >75% repigmentation rates of 91% in SV vs 53% in NSV), provides partial clinical support for the mosaicism theory (Gupta and Kumar, 2003; Zhang et al, 2021). Successful transplantation could require the replacement of the destroyed mutant melanocytes in the SV lesion

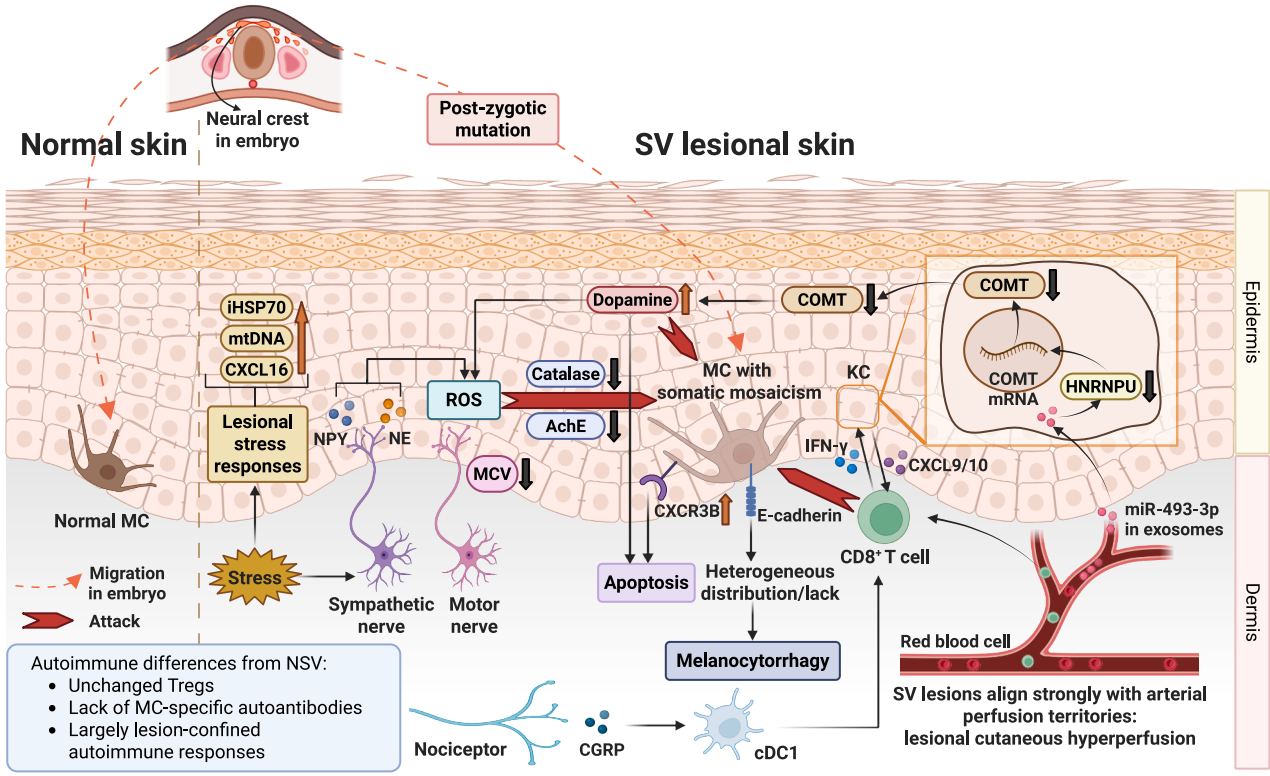

Figure 2. Integrative pathogenesis of SV. Somatic mosaicism: A postzygotic sequence variant generates a clone of genetically susceptible melanocytes with intrinsic abnormalities, distributed along embryonic melanoblast migration pathways. Neurovascular dysfunction: Local nerve hyperactivity leads to altered nerve conduction, vasomotor instability, and the release of neurotransmitters (eg, NE, NPY, CGRP). These molecules induce oxidative stress, potentiate local immune responses, and damage susceptible melanocytes. SV lesions often align with arterial perfusion territories. Localized autoimmunity: Local stress responses and CXCR3B overexpression trigger localized autoimmunity. The susceptible mosaic melanocytes are targeted by localized autoimmune responses, which are characterized by the infiltration of $CD8^+$ T cells and IFN-γ production and potentially initiated and amplified by exosomal miR-493-3p and neuroimmune crosstalk. Oxidative stress and melanocyte dysfunction: Local accumulation of ROS and dopamine, coupled with reduced antioxidant defense, directly damages melanocytes. Altered expression of E-cadherin disrupts melanocyte adhesion. This figure was created with BioRender.com. AchE, acetylcholinesterase; cDC1, conventional type 1 dendritic cell; CGRP, calcitonin gene-related peptide; iHSP70, inducible HSP70; KC, keratinocyte; MC, melanocyte; MCV, motor nerve conduction velocity; NE, norepinephrine; NPY, neuropeptide Y; SV, segmental vitiligo.

with genetically normal melanocytes harvested from an unaffected donor site. These grafted cells potentially inherently evade the localized immune responses directed against the original mosaic cells. However, potential selection bias (eg, variable proportions of facial vitiligo) and SV's inherent characteristics (lower autoimmune activity and lower recurrence rates than NSV) also contribute to favorable surgical results.

In addition to SV, other localized mosaic inflammatory disorders (eg, linear morphea, lichen sclerosus, and lichen striatus) also share characteristic Blaschko-linear distribution, early onset, and self-limited progression (Kahle et al, 2023; Lee et al, 2014; Speeckaert et al, 2020). The frequent co-occurrence of SV with these disorders further underscores the concept of immune-mediated targeting of genetically distinct cell populations (Kahle et al, 2023; Kim et al, 2016; Weisberg et al, 2008; Yadav et al, 2014). This colocalization of distinct mosaic disorders affecting different cell lineages strongly suggests that the underlying somatic sequence variant event creates a susceptible skin microenvironment permissive to localized autoimmunity rather than the pathology being solely cell-type specific. In addition, Sarma (2020) discovered that 58.6% of facial and cervical NSV lesions align with Blaschko's lines and embryonic pigmentary segments. These mosaic patterns indicate that segmental embryonic melanoblast heterogeneity dictates regional susceptibility to vitiligo, challenging the traditional concept that mosaicism is restricted to segmental disease (Sarma, 2020).

Neurovascular contributions

Emerging evidence underscores the crucial role of neurovascular dysfunction in SV pathogenesis. The dysregulation of sympathetic nervous system and motor nerve manifests locally in SV lesions. Motor nerve conduction velocity is significantly slowed in affected limbs compared with that in contralateral healthy sides (55.30 ± 6.74 vs 56.63 ± 7.43 m/s; $P = .006$), particularly in stable disease phases, indicating regionally restricted demyelination (Zhou et al, 2016). This aligns with findings of cutaneous hyperperfusion—marked by a nearly threefold increase in blood flow and elevated α/β-adrenoreceptor responses, specifically in SV lesions, with no alterations observed in plasma catecholamine levels or in the density of adrenergic receptors on blood cells, suggesting localized sympathetic hyperactivity rather than systemic catecholamine imbalance (Wu et al, 2000).

Neurotransmitters could induce local immune responses and further exacerbate melanocyte vulnerability: when the body is stimulated by stress (such as mental tension), cutaneous sympathetic nerve terminals release norepinephrine (NE) and neuropeptide Y (NPY), with plasma NPY levels closely correlated with NE elevation (Fu et al, 2025; Pernow et al, 1986). NE binds to the β2-adrenergic receptor, participates in oxidative stress, and ultimately damages melanocytes (Fu et al, 2025). NPY upregulates ROS and destroys melanocytes in the skin and hair follicles through direct and indirect cytotoxicity (Yu et al, 2012). Moreover, NPY also modulates the hypothalamic–pituitary–adrenal axis to maintain emotional homeostasis (Thorsell, 2010). Another neuropeptide, vasoactive intestinal peptide, can induce antigen-specific Tregs (identified as being central to the development of melanocyte destruction) and can shift the T helper (Th)1/cytotoxic T-cell 1 balance (Ganea et al, 2015; Giri et al, 2020; Martins et al, 2020). Another neuropeptide, nociceptor-derived calcitonin gene-related peptide (CGRP), is elevated in the lesional skin of patients with vitiligo and directly enhances dermal type 1 conventional dendritic cell (cDC1) function through CALCRL–RAMP1 receptors, strengthening cDC1-$CD8^+$ T-cell interactions to drive melanocyte destruction (Yang et al, 2025).

Anatomically, SV lesions correlate strongly with arterial perfusion territories. Comprehensive mapping of 140 SV lesions revealed that 72% exhibit exact alignment with underlying arterial blood supply zones, such as the facial artery in craniofacial SV, contrasting with only 12% adherence to classic dermatomes (Benzekri et al, 2024). Thermographic studies corroborate this, showing significant thermal asymmetry ($P < .001$) between active SV lesions and the contralateral side, indicating perfusion abnormalities (Benzekri et al, 2024). Histology revealed periarterial inflammatory infiltrates and degenerative changes in periarterial nerves, implicating the vessel wall-neural plexus as an early target (Benzekri et al, 2024). Integrating virological observations, Gauthier et al (2023) propose that latent varicella-zoster virus reactivation within sympathetic ganglia allows viral particles to migrate along periarterial nerves, inducing transient vasomotor instability followed by melanocyte death confined to the arterial territory. Spatial transcriptomics of vitiligo lesions confirms the colocalization of $CGRP^+$ nerve fibers with $CD8^+$ T cells and cDC1s in the dermis, where CGRP promotes autoreactive T-cell responses, indicating the neuroimmune crosstalk in depigmented skin (Yang et al, 2025). These findings highlight the interplay between cutaneous perfusion, sympathetic nerve dysfunction, and localized melanocyte loss, emphasizing neurovascular-mediated melanocyte damage.

Nevertheless, controversy persists regarding causality. Chemical sympathectomy using 6-hydroxydopamine in murine models failed to alter SV progression, suggesting that sympathetic dysfunction may be a secondary phenomenon rather than a primary driver (Hu et al, 2025). It implies that neurovascular changes could potentiate (but not initiate) immune-mediated melanocyte destruction. However, the melanoma–Treg induction model underlying this conclusion has limitations, including the absence of $CD4^+$ T-cell–mediated immune responses (eg, Th1/Th17 responses) and the lack of stress-induced or neurotransmitter-level assessments, which may affect the comprehensiveness and clinical relevance of the findings (Peng and Wang, 2025). CGRP receptor antagonism (eg, rimegepant) can alleviate depigmentation in vitiligo by blocking nociceptor–cDC1 interactions and reducing $CD8^+$ T-cell infiltration, yet requires concomitant immune modulation for sustained efficacy, highlighting the auxiliary role of neurovascular in amplifying established autoimmunity (Yang et al, 2025). Thus, SV pathogenesis likely represents a convergence of neurovascular dysregulation and focal autoimmune responses targeting genetically susceptible melanocyte clones.

Autoimmune mechanisms involved in SV

Emerging evidence indicates that SV is driven by a compartmentalized autoimmune reaction that contrasts sharply with the systemic immune activation characteristic of NSV. Although both entities share the common endpoint of melanocyte loss, the immunological choreography is distinct. Serum cytokine profiles and peripheral immune cell analyses reveal no evidence of increased systemic immunity in SV (Willemsen et al, 2022). Patients with SV maintain normal numbers of circulating Tregs and show no increase in antibody-producing plasmablasts compared with healthy controls. Conversely, NSV presents with elevated levels of CXCL9, CXCL10, IFN-γ, IL-2, IL-6, and IL-17 in peripheral blood (Aulakh et al, 2025; Xu et al, 2022b), accompanied by a marked systemic reduction in Tregs and expansion of melanocyte-specific $CD8^+$ effector T cells that circulate systemically (Willemsen et al, 2022). NSV is also characterized by robust humoral responses against melanocyte antigens such as tyrosinase, TRP-1, and HSP90 (Waterman et al, 2010; Willemsen et al, 2022). Notably, autoantibody screens using phage-displayed melanocyte antigens detect serological reactivity in 51% of patients with NSV but in none with SV (Waterman et al, 2010). Transcriptional profiling of peripheral blood leukocytes further highlights the differences between SV and NSV. Comparative microarray data demonstrate that SV is enriched for adaptive immune response genes, cytokine–cytokine receptor interactions, and chemokine signaling pathways (Wang et al, 2016). In contrast, NSV exhibits a pronounced innate immune signature, with upregulation of IFN-γ–mediated signaling, toll-like receptor cascades, and B-cell differentiation programs (Wang et al, 2016). Notably, miRNA is involved in the destruction of melanocytes in SV. Circulating exosomes enriched in miR-493-3p are preferentially internalized by keratinocytes within the SV-affected segment, where the miRNA directly targets *HNRNPU* to downregulate catechol-O-methyltransferase (COMT) (Li et al, 2022). The resulting local accumulation of dopamine generates ROS and triggers melanocyte apoptosis (Li et al, 2022). Thus, the autoimmune process in SV remains largely lesion confined, whereas NSV involves a widespread immunological activation.

At the tissue level, immunofluorescence studies reveal dense perilesional infiltrates of IFN-γ–producing $CD4^+$ Th1 and $CD8^+$ cytotoxic T-cell 1 cells in both active SV and mild-to-moderate vitiligo, but the magnitude of infiltration and cytokine expression are markedly lower in SV (Xu et al, 2022b). However, another study found that SV manifests as a combined effect of immune activation throughout the skin

(elevated IFN-γ, CXCL9/CXCL10, matrix metalloproteinase 9 [MMP9], and loss of E-cadherin in both lesional and nonlesional areas), and localized stress responses specific to the lesions (elevated mtDNA, iHSP70, and CXCL16) (Passeron et al, 2022). The research also supports the spatial limitation of SV autoimmune response: overexpression of CXCR3B specifically in melanocytes at lesion sites triggers localized autoimmunity by inducing apoptosis, which may be the core mechanism driving segmental depigmentation and offers potential targets for therapeutic intervention (Passeron et al, 2022). In contrast, Tulic et al (2019) showed that CXCR3B is upregulated in nonlesional melanocytes from patients with NSV, which triggers apoptosis and activates T cells through the IFN-γ—CXCL10 axis. When NSV is combined with autoimmune thyroid disease or alopecia areata, the expression of *CXCR3* mRNA in PBMCs and serum CXCL10 levels are significantly elevated (highest in those with combined autoimmune thyroid disease and alopecia areata) (Zhang et al, 2019). The abnormal activation of the CXCL10/CXCR3 axis is a specific characteristic of NSV combined with autoimmune diseases (Zhang et al, 2019).

The epidemiological corollary of these mechanistic differences is a markedly lower prevalence of systemic autoimmune comorbidities in SV. Large prospective cohorts indicate that thyroid autoantibodies, alopecia areata, and type 1 diabetes are over-represented in NSV, whereas patients with SV exhibit significantly fewer extracutaneous autoimmunity (Ezzedine et al, 2011; Willemsen et al, 2022).

In summary, SV and NSV represent immunologically distinct entities with divergent autoimmune mechanisms. SV manifests as a mosaic, largely lesion-restricted autoimmune disorder, resulting in melanocyte destruction confined to specific areas without systemic immune dysregulation. In contrast, NSV features systemic autoimmunity characterized by broad T-cell dysregulation, polyclonal autoantibody production, and innate immune activation that predisposes to autoimmune comorbidities. These differences are reflected at transcriptional, cellular, and clinical levels. Understanding these mechanistic divergences provides a framework for subtype-specific research and therapeutic development.

Oxidative stress and melanocyte dysfunction

Accumulating evidence highlights oxidative stress as a critical pathogenic component in both SV and NSV. ROS cause melanocyte destruction through direct cytotoxic effects, inactivation of key enzymes, and alteration of melanocyte structural antigens, thereby triggering a specific adaptive immune response against melanocytes (Fu et al, 2025). Patients with vitiligo exhibit significant epidermal oxidative stress characterized by hydrogen peroxide (H_2O_2) accumulation up to 10^{-3} M, leading to inactivation of key enzymes (eg, catalase and acetylcholinesterase) (Schallreuter et al, 2004, 1991). H_2O_2 removal restores acetylcholinesterase expression and facilitates repigmentation, providing evidence for the crucial role of oxidative stress in vitiligo pathogenesis (Schallreuter et al, 1991). Other studies found that epidermal H_2O_2/peroxynitrite ($ONOO^-$)-mediated oxidative stress is the key pathological mechanism, characterized by biopterin accumulation, deficiency of antioxidant enzymes (catalase, thioredoxin reductase, methionine sulfoxide reductases A/B), and protein oxidative damage (Schallreuter et al, 2013). Compared with that of NSV, systemic oxidative stress contributes weakly and limitedly to the pathogenesis of SV (Dellatorre et al, 2023; Li et al, 2021; Schallreuter et al, 2013). Significantly elevated stress-induced markers (such as mtDNA, iHSP70, and CXCL16) in SV are confined to the perilesional skin (Dellatorre et al, 2023; Passeron et al, 2022). Systemic antioxidant status analysis further reveals that SV is primarily associated with a specific reduction in catalase activity, distinguishing it from glutathione peroxidase/reduced glutathione deficiency observed in NSV (Shajil and Begum, 2006). In addition, SV exhibits elevated levels of superoxide dismutase (SOD) and increased lipid peroxidation (Shajil and Begum, 2006). Whether these findings are related to the primary etiology or secondary phenomena induced by inflammation remains unclear. To date, there is a lack of reproducible results demonstrating the effective treatment of SV with antioxidants.

Other factors can also lead to melanocytes' vulnerability to oxidative damage and dysfunction. Mitochondria play an indispensable role in the pathogenesis of vitiligo. Melanin formation requires substantial energy, and mitochondria serve as the source of adenosine triphosphate. Mitochondrial dysfunction could impede melanin production, promote oxidative stress in melanocytes by generating ROS, and alter the balance of reduction—oxidation (redox) reactions (Katz and Harris, 2021). Elevated oxidative stress in vitiligo melanocytes drives the accumulation of somatic mtDNA variants and subsequent mtDNA release into the cytosol (Sant'Anna-Silva et al, 2024). This cytosolic mtDNA activates the cGAS—STING signaling pathway, triggering the production of IFN regulatory factor (IRF)3, IRF7, and the NF-κB pathway that initiate an autoimmune response against melanocytes (Sant'Anna-Silva et al, 2024). Therapeutic targeting of mitochondrial oxidative stress with specific antioxidants (eg, SOD2) or NRF2 activators effectively suppresses this pathway, suggesting a promising mechanistic and treatment strategy for vitiligo (Sant'Anna-Silva et al, 2024). In addition, interactions between mitochondria and melanosomes exist to maintain normal skin pigmentation (Wu and Hammer, 2014). Allouche et al (2021) identified nicotinamide nucleotide transhydrogenase (NNT) as a mitochondrial redox switch that controls pigmentation independently of UVB/microphthalmia-associated transcription factor, by modulating tyrosinase ubiquitination and melanosome maturation; NNT inhibition increases oxidative stress and eumelanin, suggesting a direct mechanistic bridge between mitochondrial oxidative stress and pigmentary defects (Allouche et al, 2021). miRNA dysregulation further exacerbates oxidative stress and dysfunction: miR-493-3p upregulation in SV perilesional skin elevates dopamine, inhibiting melanin production and promoting ROS accumulation and melanocyte apoptosis (Li et al, 2022). Impaired cell adhesion function due to E-cadherin deficiency is the basis of melanocyte detachment (melanocytorrhagy) in SV. The altered distribution of E-cadherin/β-catenin destabilizes melanocyte-keratinocyte adhesion, rendering cells vulnerable to oxidative stress and mechanical stress (Grill et al, 2018). This defect is intrinsic to E-cadherin, because P-cadherin expression remains normal (Grill et al, 2018). Nevertheless, no

difference was found between SV and contralateral skin in MMP9 and E-cadherin levels, suggesting that this mechanism is not specific to SV and is observed in all types of vitiligo (Passeron et al, 2022).

POTENTIAL THERAPEUTIC PARADIGMS

According to the 2023 guidelines issued by the International Vitiligo Working Group, the overarching treatment objectives for SV encompass halting disease progression, inducing repigmentation, enhancing quality of life, and facilitating personalized therapeutic plans through shared decision making between clinicians and patients (van Geel et al, 2023). With regard to treatment principles, active SV—defined by emergence of new lesions or expansion of existing ones in previous 12 months—should be managed primarily with localized interventions, including topical corticosteroids or calcineurin inhibitors, in conjunction with phototherapy such as narrowband UVB (NB-UVB), aimed at suppressing inflammation (van Geel et al, 2023). Combination therapy with 308-nm excimer laser, topical tacrolimus, and short-term systemic corticosteroids has provided favorable results in SV (Bae et al, 2015). Interestingly, duration below 12 months and absence of poliosis were associated with significantly better responses.

In contrast, stable SV—characterized by the absence of disease progression for at least 12 months—should focus on repigmentation strategies, which may include sustained topical therapy combined with phototherapy or, in cases of localized and treatment-resistant lesions, surgical modalities (van Geel et al, 2023). However, conventional strategies, primarily topical pharmacotherapy and phototherapy, demonstrate markedly reduced efficacy in patients with SV compared with that in those with NSV. Consequently, the exploration of emerging therapeutic modalities, including advanced surgical techniques and molecularly targeted therapies, holds particular significance for this patient group. This review summarizes the current and potential treatment strategies for SV (Figure 3).

Biomarkers for diagnosis and treatment of SV

As previously described, TWEAK and S100B serve as key biomarkers for differentiating SV from NSV and active from stable disease, respectively (El-Taweel et al, 2021; Shabaka et al, 2022). Furthermore, poliosis, halo nevi, and truncal lesions represent important indicators for SV progression to MV (Ezzedine et al, 2012a; Lee et al, 2011). Serum analyses reveal significantly elevated CXCL10 levels in progressive SV, whereas CXCL9 shows a nonsignificant upward trend (Aulakh et al, 2025). In recent years, circulating exosomal miRNAs have emerged as characteristic molecules in dermatological diseases (Li et al, 2022). Notably, plasma exosomal miR-493-3p is significantly elevated in patients with SV compared with that in healthy controls and further increases during active disease (Li et al, 2022). Mechanistically, miR-493-3p promotes dopamine release from keratinocytes through the miR-493-3p−HNRNPU−COMT axis, thereby enhancing oxidative stress and apoptosis in melanocytes (Li et al, 2022). This identifies miR-493-3p as a promising therapeutic target in SV.

Regarding treatment prediction, patients demonstrating a favorable response to NB-UVB combined with tacrolimus had significantly shorter disease duration than poor responders (2.5 vs 11.5 years, $P = .046$), despite comparable demographics and disease characteristics (Yang et al, 2021). Subsequent transcriptomic analysis identified 68 differentially expressed genes (eg, upregulated *CXCL10*, *FCRL3*, *TCR*) predictive of treatment response (Yang et al, 2021). A prospective pilot study suggested that restoration of impaired sympathetic function may underlie visible light efficacy in SV, with changes in skin blood flow under cold stress before and after irradiation potentially serving as a response predictor (Yu et al, 2011). For relapse prediction, significantly elevated serum levels of IFN-γ, CXCL9, CXCL10, CXCL11, and IL-6 were observed in recurrent versus stable vitiligo ($P = .001$, .003, <.001, .002, and .026, respectively) (Liu et al, 2025). Receiver operating characteristic analysis further confirmed the predictive capacity of these cytokines for relapse, with area under the curve values of 0.806, 0.773, 0.896, 0.785, and 0.709, respectively (Liu et al, 2025).

Limitations of conventional therapies

Topical interventions predominantly employ corticosteroids and calcineurin inhibitors; however, clinical evidence supporting their efficacy in SV remains limited and inconsistent. In a pediatric SV cohort (n = 9), twice-daily 1% pimecrolimus cream demonstrated efficacy and tolerability over 3 months (Shim et al, 2013), whereas another study (n = 38) using 0.05% clobetasol propionate (twice daily with 6-weekly 2-week interruptions) reported partial response in most patients (30 of 38), yet only 34% (13 of 38) achieved >50% repigmentation (Khalid and Mujtaba, 1998). Research in patients with SV (n = 6) indicated a 66.7% response rate to twice-daily 0.1% tacrolimus ointment, with facial involvement showing higher responsiveness (80%) and head/neck regions exhibiting superior repigmentation versus trunk/limbs (Xu et al, 2009). In contrast, a randomized controlled trial (RCT) (n = 60) comparing 6-month regimens of twice-daily 0.1% tacrolimus with once-daily 0.05% fluticasone propionate concluded that both agents yielded suboptimal repigmentation despite minimal adverse effects (eg, erythema, telangiectasia) (Kathuria et al, 2012). Collectively, these findings underscore the need for further validation of topical modalities' efficacy in SV through large-scale RCTs.

Phototherapy constitutes another cornerstone of SV management. A retrospective analysis revealed that NB-UVB yielded a lower mean Vitiligo Area Scoring Index improvement in SV (−40.0% ± 28.3%) than in NSV (−50.0% ± 31.0%) (Silpa-Archa et al, 2019). Excimer light exhibits efficacy in pediatric SV (n = 26), particularly among patients with shorter disease duration (<6 months) (Majid and Imran, 2020). Early initiation of 308-nm excimer laser therapy correlates with superior repigmentation outcomes, with prolonged treatment duration and higher cumulative energy enhancing therapeutic response (Do et al, 2011). Combination therapy using 308-nm excimer laser with YiqiQubai granules further augmented clinical efficacy (Zhang et al, 2017). Notably, poliosis substantially compromises excimer laser responsiveness irrespective of vitiligo subtype ($P < .01$) (Bae et al, 2015; Kim et al, 2016). Thus, phototherapeutic

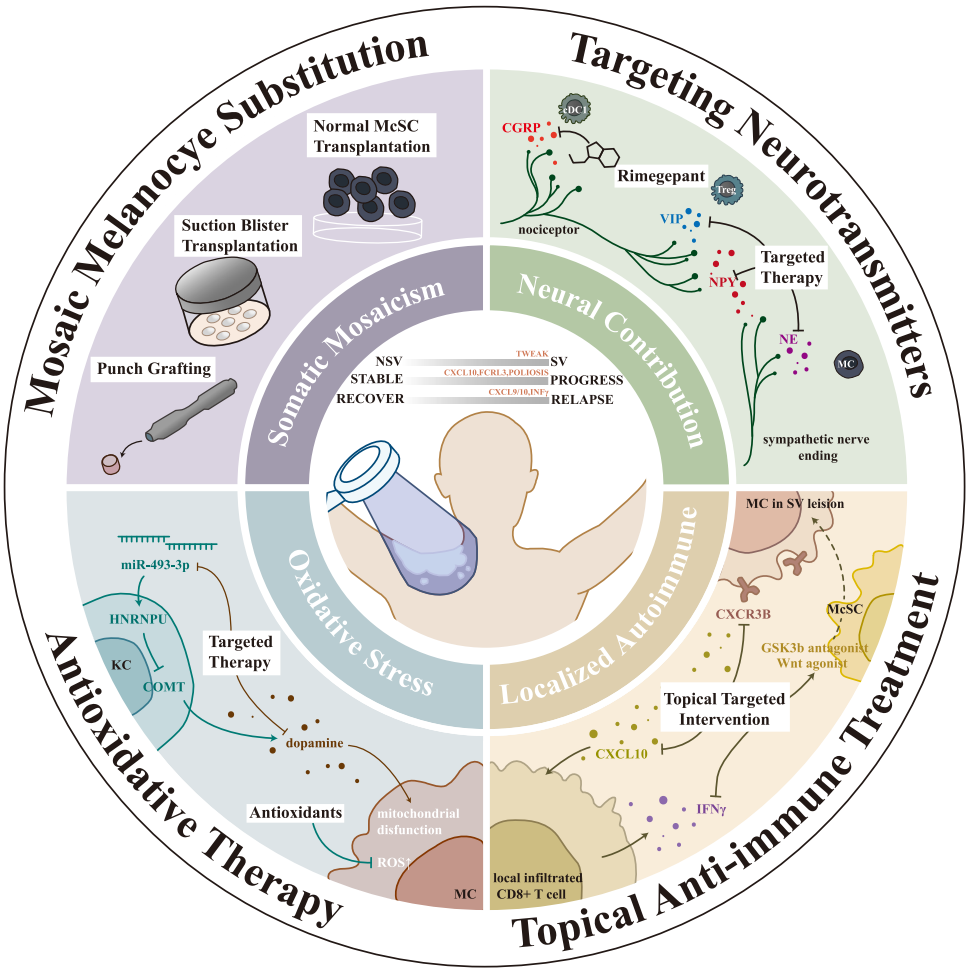

Figure 3. Current management and future treatment perspectives in SV. The central section illustrates biomarkers for SV diagnosis. The outer ring summarizes existing treatments and potential therapeutic targets on the basis of 4 proposed mechanisms underlying SV. Somatic mosaicism: Normal McSC transplantation, suction blister transplantation, and punch grafting. Neural contribution: Neurotransmitter-targeted therapy. Localized autoimmune: Cytokine and receptor-targeted therapy. Oxidative stress: Targeted and antioxidant therapies. cDC1, conventional type 1 dendritic cell; CGRP, calcitonin gene-related peptide; COMT, catechol-O-methyltransferase; KC, keratinocyte; MC, melanocyte; McSC, melanocyte stem cell; NE, norepinephrine; NPY, neuropeptide Y; Treg, regulatory T cell; VIP, vasoactive intestinal peptide; TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

outcomes in SV are critically constrained by (i) disease chronicity, (ii) treatment initiation timing, (iii) cumulative energy dosage, and (iv) combination strategies, resulting in pronounced interpatient heterogeneity and consistently inferior efficacy relative to NSV. Beyond these approaches, helium-neon laser therapy shows emerging potential for repigmentation through normalization of dermal perfusion and adrenergic receptor dysfunction, although additional clinical validation is required (Wu et al, 2008).

These data clearly underline that medical approaches for SV provide significantly better outcome when initiated in the first year after the onset of the disease. This strongly argues in favor of an early intervention for achieving optimal results.

Surgical approaches

Surgical intervention represents a viable alternative for medical therapy-refractory SV during stable disease phases. Established modalities include punch grafting, hair follicle transplantation, split-thickness epidermal grafting, suction blister epidermal grafting, and melanocyte–keratinocyte transplantation procedure (MKTP) (Khalili et al, 2022). A prospective cohort study with a mean follow-up of 5.2 years reported excellent repigmentation in 78% (7 of 9) of patients with SV treated with 2-mm punch grafting, exceeding outcomes in NSV (17 of 61) (Fongers et al, 2009). Notably, a modified autologous cultured epidermal grafting technique developed by Li et al (2024) achieved 82.81% overall efficacy (1754 of 2118) and 64.87% repigmentation rate across 726 patients, surpassing conventional surgical outcomes (52.69%) with superior efficacy in SV. These findings highlight the greater therapeutic potential of surgical approaches for SV than for NSV.

Autologous cell transplantation constitutes a reliable modality for stable SV. Systematic review evidence indicates ≥80% excellent and stable repigmentation rates across multiple anatomical sites, with cultured melanocyte transplantation demonstrating superior efficacy over noncultured suspension transplantation (NCST) (Souroujon et al, 2023). Retrospective analysis of 2283 patients with vitiligo with long-term follow-up further confirms enhanced repigmentation efficacy of MKTP in SV (400 of 606 cases) (Zhang et al, 2021). Regarding efficacy determinants, higher donor skin expansion ratios inversely correlate with repigmentation percentages after NCST, warranting consideration during protocol optimization (Narayan et al, 2021). Furthermore, an RCT established that superficial full-surface ablation at 209- and 144-μm depths provides superior recipient bed preparation for cell suspension grafting, compared with fractional carbon dioxide laser (Lommerts et al, 2017).

Ongoing refinements aim to optimize cell-based transplantation. An RCT indicates that automated cell-harvesting devices (eg, ReCell) streamline NCST procedures,

significantly improving repigmentation in stable SV and piebaldism with favorable safety profiles (Komen et al, 2015). Kumar's simplified "Four Chamber" method offers a cost-effective, clinic-based NCST alternative requiring no specialized laboratory infrastructure (Kumar et al, 2014). Esmat et al (2020) reported that supplementing melanocyte–keratinocyte cultures with basic fibroblast GF and cyclic adenosine monophosphate significantly enhances MKTP repigmentation outcomes (Esmat et al, 2020). However, safety data on phenotypic and genetic changes of melanocytes under culture conditions, along with optimal population doubling before grafting, are still needed before using cultured melanocytes in clinical practice. Notably, rare suboptimal responses—including perigraft hypopigmentation or Koebner phenomenon—may occur after transplantation in some patients with SV, necessitating mechanistic studies to elucidate MKTP failure pathways in these subsets (Isedeh et al, 2015). Moreover, a recent study failed to demonstrate that adjunctive use of ruxolitinib cream (a Jak inhibitor) improved repigmentation in difficult-to-treat areas after epidermal cell suspension grafting (Dugourd et al, 2025). This suggests that in those areas, there are local factors that prevent or decrease the differentiation, proliferation, and survival of melanocytes. Present grafting procedures primarily transfer keratinocytes and melanocytes, whereas the dermis, particularly fibroblasts, remains unchanged. Because there is growing evidence for the role of dysfunctional fibroblasts in vitiligo pathogenesis (Xu et al, 2022b), this unaltered dermal niche may limit treatment response in some locations such as acral sites.

Targeted therapeutic strategies

The established centrality of the IFN-γ–Jak1–signal transducer and activator of transcription 1–CXCL9/10 axis in NSV pathogenesis has catalyzed the development of targeted therapy, and topical ruxolitinib, a selective Jak1/2 inhibitor, has recently been approved in the United States for the treatment of NSV in patients aged >12 years (Tavoletti et al, 2023). qPCR analysis revealing elevated CXCL9/10 expression in both lesional and nonlesional SV skin implicates Jak pathway involvement in SV pathophysiology (Passeron et al, 2022). Nevertheless, SV-specific targeted strategies remain scarce. Complete repigmentation was achieved in a patient with SV aged 4 years after 6 months of twice-daily topical tofacitinib combined with thrice-weekly home-based NB-UVB after corticosteroid failure (Olamiju and Craiglow, 2020). Similarly, a significant lesion reduction occurred in a patient with SV and comorbid alopecia areata aged 9 years treated with upadacitinib plus NB-UVB (Mu et al, 2024). These preliminary clinical cases suggest that Jak inhibitors may represent a viable SV treatment option but warrant validation in larger controlled studies.

Beyond Jak inhibition, enhancing melanocyte repigmentation through melanocyte stem cell (McSC) differentiation regulators constitutes another strategic avenue. Wnt/β-catenin activation promotes McSC differentiation, whereas Kit signaling facilitates melanocyte migration during UVB exposure, positioning topical Wnt agonists (or GSK3 antagonists) as promising repigmentation therapeutics (Regazzetti et al, 2015; Speeckaert and van Geel, 2017). As SV pathogenesis mechanisms—including neuroimmune crosstalk, melanocyte antigen chimerism, and exosomal miRNA dysregulation—continue to be elucidated, promising targeted therapies with enhanced specificity, such as CXCR3B antagonists and neuroimmune axis modulators, are anticipated to emerge.

Collectively, the preceding sections have delineated the fundamental differences between SV and NSV. These distinctions are comprehensively summarized in Table 1, which contrasts the 2 subtypes across key domains, including

Table 1. Comparison between SV and NSV

Domains	SV	NSV
Epidemiology	Accounts for 5–27.9% of vitiligo cases	Accounts for 72.1–95% of vitiligo cases.
Comorbidities	Lower rates of autoimmune diseases (eg, positive rate of thyroid antibodies is 1.7%) and disease activity markers (eg, hypopigmented borders, confetti-like depigmentation, Koebner phenomenon)	Higher rates of autoimmune diseases (eg, positive rate of thyroid antibodies is 29.6%) and disease activity markers.
Clinical presentation	Unilateral, commonly involving head/face (49.3%) and trunk (33.8%). Higher rates of poliosis (45.2%) and lower rates of halo nevi (10.2%)	Symmetric/generalized depigmentation Higher rates of halo nevi (45.8%)
Evolution	Stabilizes within 1–2 years after rapid progression, with a relatively low recurrence rate (11.9–21.1%). Recurrences mostly limited to the original anatomical regions	Progressive course Recurrence still likely even after long-term stabilization Relapses occur in 40–50% of cases within a year after repigmentation
Differential diagnosis	Needs to be differentiated from SND: SND mostly occurs before the age of 10 y, with serrated borders, wider vertical distribution, and grayish white under Wood's lamp, and RCM shows the presence of melanocytes.	Needs to be differentiated from other autoimmune diseases or postinflammatory hypopigmentation
Pathological mechanisms	Somatic mosaicism, neurovascular dysfunction, local autoimmunity, and oxidative stress	Systemic autoimmunity, activation of the IFN-γ–CXCL9/10 axis, and T-cell dysregulation.
Treatment methods	Poor response to conventional treatments (eg, topical corticosteroids, phototherapy), especially after the first year of evolution. Better response to surgical transplantation (eg, MKTP).	Good response to phototherapy and Jak inhibitors (eg, ruxolitinib)
Treatment outcomes	Surgical transplantation has a high repigmentation rate (>75% repigmentation rate, 91%), but the efficacy is poor in cases with poliosis. Jak inhibitors combined with phototherapy are effective in individual cases.	Phototherapy and immunomodulatory treatments respond relatively well, but recurrence is common.

Abbreviations: MKTP, melanocyte–keratinocyte transplantation procedure; NSV, nonsegmental vitiligo; RCM, reflectance confocal microscopy; SND, segmental nevus depigmentosus; SV, segmental vitiligo.

epidemiology, comorbidities, clinical presentation, evolution, differential diagnosis, pathological mechanisms, and treatment.

CONCLUSION

SV is now unequivocally established as a distinct clinicopathological entity, characterized by its unilateral distribution, early and rapid onset, and predilection for craniofacial regions. Clinically, SV exhibits accelerated stabilization (typically within 1–2 years), high-frequency leukotrichia, and low systemic autoimmunity yet paradoxically demonstrates anatomically restricted recurrence that challenges traditional notions of inherent stability. These unique phenotypes, alongside diagnostic and classification dilemmas, are argued to have their foundation in its pathogenesis: somatic mosaicism drives lesion distribution along embryonic melanoblast migration routes, neurovascular dysfunction amplifies localized immune attack, localized autoimmunity ensures targeted melanocyte destruction, and the vulnerability to oxidative stress.

Therapeutic limitations of conventional approaches (topical immunomodulators, phototherapy), evidenced by merely about 7.3% achieving significant repigmentation, contrast with the exceptional efficacy of surgical interventions such as autologous melanocyte–keratinocyte transplantation, in which replacement of mosaic melanocytes validates SV's clonal etiology. Emerging biomarkers (serum TWEAK for SV/NSV differentiation [100% sensitivity], exosomal miR-493-3p regulating dopamine-induced apoptosis, and CXCL9/10 predicting recurrence) herald precision diagnostics, whereas nascent targeted strategies offer mechanism-based therapeutic innovation. Future studies are supposed to prioritize multiomics integration to delineate SV-specific genetic–epigenetic–neuroimmune networks: refine disease classification by anatomical subtypes and immune phenotypes, seek SV-specific biomarkers, explore the somatic sequence variant–immune interaction network and neuroimmune-vascular crosstalk, and ultimately translate pathogenesis mechanisms into targeted therapeutic intervention. SV emphasizes that a clear mechanistic understanding of clinical heterogeneity drives more precise diagnosis, treatment, and prognosis in clinical practice.

ETHICS STATEMENT

The images of patients presented in Figure 1 were obtained during the course of routine clinical care. Their use for publication in this review is in compliance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the patients (or their legal guardians) specifically for the publication of their identifiable images.

DATA AVAILABILITY STATEMENT

No data were used to support this study.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CZ, TP; Funding Acquisition: CZ; Project Administration: CZ; Visualization: NS, QF, YX, YL; Writing - Original Draft Preparation: NS, QF, YX, YL, TP, CZ; Writing - Review and Editing: NS, QF, TP, CZ

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