A Scoping Review of the Methodology Used in Studies of Genetic Influences on the Development of Keloid or Hypertrophic Scarring in Adults and Children After Acute Wounding

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Significance: Keloid and hypertrophic scarring are common following acute wounds. However, the variability in scarring outcomes between individuals and in particular, the association between genetic factors and scarring, is not well understood. This scoping review aims to summarize the methodology used in studies of genetic influences on the development of keloid or hypertrophic scarring in adults and children after acute wounding. The objectives were to determine the study designs used, the characteristics of participants included, the tools used to assess scarring and the length of follow-up after wounding.
Recent Advances: The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Medline, Excerpta Medica Database (EMBASE), Web of Science, Biosciences Information Service (BIOSIS), Prospective Register of Systematic Reviews (PROSPERO), The Human Genetic Epidemiology (HuGE) Navigator (database of genetic association studies), and the genome-wide association study Catalog were searched from January 2008 to April 2020. Cohort studies and case–control studies that examined the association between one or more genetic variations and the development of keloid or hypertrophic scarring were eligible for inclusion. A narrative synthesis that grouped studies by wound type was conducted.
Critical Issues: Nine studies met the inclusion criteria (five in burns, four surgical wounds, and none in other types of acute wounds). Seven assessed hypertrophic scarring, one keloid scarring, and one both scar types. Seven studies used a prospective cohort design. All studies used subjective methods (clinician or patient observation) to assess scarring. There was considerable variation in how scar scales were operationalized.
Future Directions: This review identified a small body of evidence on genetic susceptibility to scarring after acute wounding. Further studies are needed, and in a wide range of populations, including patients with wounds caused by trauma.

Keywords: cicatrix, hypertrophic, keloid, genetic association study, polymorphism, single nucleotide, systematic review

SCOPE OF THE REVIEW AND ITS SIGNIFICANCE

This scoping review (a type of research synthesis that aims to map the literature on a particular topic) focuses on the methodology used in studies of the association of genetic variants and the development of hypertrophic or keloid scarring following acute wounding. It considers the study designs used, characteristics of included participants and methods used to assess scarring. It is the first review to address these issues. The review brings together and provides an overview of the small body of evidence in the area and makes recommendations for the conduct of future studies.

TRANSLATIONAL RELEVANCE

Studies of the association between genetic variants and the development of hypertrophic or keloid scarring can increase understanding of which individuals are at risk of developing these types of scars following acute wounding. This review focuses on the methodology used in the small number of studies conducted to date and makes recommendations that will strengthen future research in the area.

CLINICAL RELEVANCE

An increased understanding of how scarring quality is influenced by genetic factors will help to enable personalized patient management in acute wound care. Scar prevention measures such as pressure therapy, splinting, and silicones could be better targeted at patients who are most at risk of hypertrophic or keloid scarring, while avoiding unnecessary treatment and hospital visits for those who do not need such measures.

BACKGROUND

Scar formation is part of the body's healing response following wounding, such as surgery, burns, lacerations, or other damage to the dermis (*e.g.*, insect bites, skin piercing, vaccinations, infection). While wound healing commonly results in some form of blemish at the site of the wounding, some individuals experience an excessive inflammatory healing phase resulting in an imbalance between the destruction and deposition of extracellular matrix metabolism, and the development of hypertrophic or keloid scarring.[1,2]

Hypertrophic scars are typically raised with a pink, purple, or red color from increased vascularization or dyspigmentation (hyper- or hypopigmentation) and they do not extend beyond the margins of the original wound.[3] Keloid scars are similar in appearance but continue to grow beyond the confines of the original wound and invade surrounding healthy skin.[4]

Studies have estimated the prevalence of hypertrophic scarring to be between 32% and 72% after burn injury[5] and between 40% and 70% following surgery.[6] Keloid scars are estimated to develop in 5–15% of wounds.[7] The impact of scarring on patients' lives is related to both physical and psychosocial effects.[8] Physical effects of scarring include pain, itch, limited range of motion, and sleep disturbances.[9] Psychological effects include reduced self-esteem and confidence and increased levels of stigmatization, anxiety, and depression.[10]

The underlying cause for the difference in scarring outcomes between individuals with similar wounds is not well understood. A better understanding of who is at high risk of hypertrophic or keloid scarring would mean that preventative treatments such as pressure garment therapy and silicone gel sheeting could be targeted appropriately, improving outcomes for these patients while also avoiding unnecessary treatments in patients that do not need them and reducing costs to health care systems.

Risk factors for hypertrophic scarring include young age, bacterial wound infection, anatomical area, skin tension, and the size and depth of the injury.[11,12] Some studies have also reported a greater risk of hypertrophic scarring in individuals with darker skin.[13,14] Keloids usually present in younger patients[3] and are more common in individuals of African, Hispanic, and Asian descent.[15] The varied incidence in ethnic populations, evidence of familial heritability, and presence in twins suggest that there may be a genetic susceptibility to keloid scarring.[4]

Genetic epidemiology is the study of the role of inherited factors in disease etiology.[16] Candidate gene and genome-wide association studies have identified genetic variants that are associated with the development of disease in clinical areas, including type 2 diabetes, autoimmune diseases, and schizophrenia.[17] To date, there has only been a small body of research on the genetic variants of scarring.

This scoping review aims to identify and summarize the methodology used in studies of genetic associations with the development of keloid or hypertrophic scarring in adults and children after acute wounding.

METHODS

A scoping review was conducted to inform the design of a longitudinal burn cohort study to assess

the impact of genetic composition on long-term scarring. Scoping reviews have been defined as "a type of knowledge synthesis, following a systematic approach to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps".[18] This type of evidence synthesis can be used to give an indication of the amount and type of evidence available and to confirm the relevance of inclusion criteria and potential review questions.[19]

This review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews.[18]

The questions addressed by the review were:

- What types of study design have been used?
- What are the characteristics of participants included in the studies?
- How long have studies followed up participants after the initial wound?
- Which tools have been used to assess scarring?

Eligibility criteria

Study designs suitable for inclusion were systematic reviews, cohort studies (prospective or retrospective), and case–control studies that examined the association between one or more genetic variations and the development of keloid or hypertrophic scarring in patients of any age or race and after any type of acute wound. Detailed inclusion criteria are shown in Table 1.

Search methods

A systematic review published in 2009 of the genetics of raised dermal scarring was identified.[20] Studies included in this review were screened for eligibility and new studies published beyond this date were sought (the exact date of the search was not published therefore searches were dated from 2008 to ensure overlap).

The following electronic databases were searched from January 1, 2008 to April 31, 2020: Medline, Excerpta Medica Database (EMBASE), Web of Science, Biosciences Information Service (BIOSIS), Prospective Register of Systematic Reviews (PROSPERO), The Human Genetic Epidemiology (HuGE) Navigator (database of genetic association studies) and the genome-wide association study (GWAS) Catalog, which captures GWASs. The searches included terms for keloid and hypertrophic scarring combined with terms for genetics (see Supplementary Appendix S1 for a sample Medline search strategy).

Reference lists of included studies and identified systematic reviews were also screened for eligibility. Internet searches were conducted and experts in the field contacted. Only English language publications were included. Conference abstracts were excluded.

Study selection

Titles and abstracts identified by the searches were screened by one reviewer (P.D.) and those that were clearly irrelevant were excluded. A random sample of 200 abstracts were selected and screened independently by a second reviewer (A.Y.). Full-text reports were obtained for all remaining references and assessed against the inclusion criteria by two independent reviewers (P.D. and A.Y.). Disagreements were resolved by discussion or, where agreement could not be reached, by consultation with a third reviewer. The selection process is shown in a PRISMA study selection flow diagram[21] in Fig. 1.

Table 1. *Eligibility criteria*

Question Components	*Details*
Study design	Systematic review Randomized controlled trial Cohort study (prospective or retrospective) Case–control study
Population/setting	Cohort study: Adults or children (>1 month old) with an acute wound of any etiology in any setting. Case–control study: Cases are individuals/tissue samples with hypertrophic or keloid scarring. Controls are individuals/tissue samples where a wound healed with normal or no scarring. Exclusions: animal studies, *in vitro* studies, case–control studies using tissue samples where the case and control have been taken from the same individual, acne (inflammatory skin condition).
Index prognostic factor	Studies may investigate specific genetic markers (genetic variant studies) or be genome wide (genome-wide association studies). Any method of genotyping will be considered.
Outcome (cohort studies) or definition of cases (case–control studies).	Presence or extent of hypertrophic or keloid scarring assessed by a verified method (*e.g.*, validated rating scale such as the VSS or POSAS).
Timing	A minimum of 6 months should have elapsed between the injury and outcome assessment

POSAS, Patient and Observer Scar Assessment Scale; VSS, Vancouver Scar Scale.

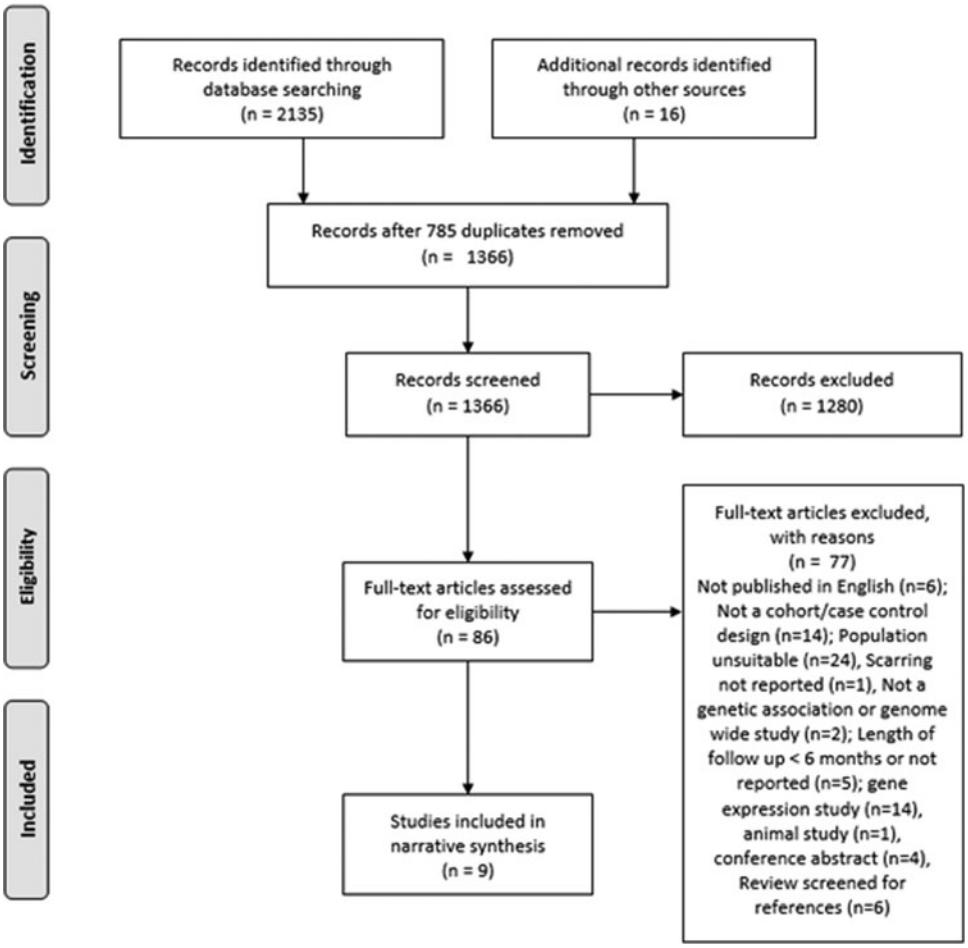

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Data extraction

Data were extracted using a standardized data extraction form by one reviewer (P.D.). Any items of uncertainty were referred to a second reviewer (A.Y.).

Data were extracted on the following: study details (author, year, country, setting, study design, length of follow up, study dates); population (sample size, inclusion/exclusion criteria, method of identification and recruitment, race, age, sex, details of wound *e.g.*, size, depth, cause of wound or burn, length of time to healing, details of treatments received *e.g.*, dressings, topical agents, surgical interventions); type of scarring (keloid or hypertrophic), including details of any measurement tool/instrument used and cutoff thresholds; candidate genes investigated and genotyping methods used; other prognostic factors for scarring considered.

As this is a scoping review, our primary aim was to provide an overview of research in the area as opposed to providing estimates of the strength of association between genetic variants and the development of keloid or hypertrophic scarring. We did not, therefore, conduct risk of bias assessment of identified studies.[19]

Synthesis

Studies were grouped by population and a narrative overview was conducted of the amount and types of evidence available, populations considered, and scarring assessments made.

RESULTS

The searches of bibliographic databases retrieved 2,135 records and a further 16 were identified from the 2009 review. After removing duplicates, 1,366 references were screened by title and abstract. Agreement between the two reviewers for the random sample of dual screened references was 98% (Cohen's κ 0.9, 95% confidence interval 0.85–0.98). Full-text reports of 86 references were obtained and screened against the prespecified eligibility criteria. Seventy-seven articles were excluded (Fig. 1).

The most common reasons for exclusion were that the study population did not all have an acute wound (*e.g.*, the use of healthy controls in a case–control study, $n = 24$, 31.2%), the study examined gene expression and not genetic variation between individuals ($n = 14$, 18.2%), and the study design did not fit the inclusion criteria (*i.e.*, not a cohort or case–control design; $n = 14$, 18.2%).

Nine studies were identified that were eligible for inclusion. Characteristics of the included studies are shown in Table 2. Five studies recruited patients with burns[22–26] and four recruited patients with surgical wounds.[27–30] No other acute wound studies were identified that met the inclusion criteria.

Study design

All five burn wound studies used a prospective cohort design where participants were recruited at the time of wounding and followed up to evaluate scarring (Table 2). All studies aimed to predict hypertrophic scarring (no studies of keloid scarring in burns patients were identified). Three looked at the association of one of more candidate genes with the development of scarring,[22,24,25] one was a GWAS[23] and one an exome-wide association study.[26] The number of participants enrolled across the five studies ranged from 300 to 953 (median 638, interquartile range [IQR] 501–717). Four studies performed a sample size calculation and reported that they were adequately powered.

Of the four surgical wound studies, two studies used a prospective cohort design.[27,30] One study was a nested case–control design[28] (all cases were identified from a cohort and matched controls selected from the same cohort) and the fourth used a case–control design.[29] Two studies focused on the role of genetic variation in the development of hypertrophic scarring,[28,30] one of keloid scarring,[29] and one of both hypertrophic and keloid scarring (although no cases of keloid scarring were detected).[27]

All of the surgical wound studies explored the association of one of more candidate genes with the development of scarring. There were no genome-wide association studies identified. The number of participants enrolled in the studies ranged from 72 to 874 (median 180, IQR 79–721). None of the studies reported a sample size calculation.

Inclusion/exclusion criteria

Inclusion criteria required burn wound participants to be adults (≥18 years) in four studies[22–25] with no age threshold in the fifth[26] (Table 2). Four studies recruited participants at risk of developing hypertrophic scarring due to delayed healing or having burns that were at least partial thickness in depth. One study excluded participants with keloid scarring (no reason given[26]).

Participants in all four acute surgical wound studies were ≥18 years. Surgery was cesarean section ($n = 2$),[27,28] cardiac surgery ($n = 1$),[29] and melanoma excision ($n = 1$).[30] One study excluded people with recorded histories of pathological scar formation or benign or malignant tumors [27] and one excluded patients whose incision overlapped with previous surgeries or trauma.[28]

Characteristics of study participants

The median age of burn wound participants ranged from 39.0 to 40.0 years in the adult studies[22–25] and was 27.9 years in the study that included children[26] (Table 3). The percentage of male participants ranged from 57.9% to 71.0% (median 68.7, IQR 62.0–71.0%). The majority of participants in the studies were white/Caucasian (median 77.5%, IQR 76–79%).

The mean age of participants across the four surgical wound studies ranged from 29.4 to 64.8 years. All participants were Chinese in one study.[27] No information about race was reported in the other three studies (Table 3 for further details of study participants). Further details of study participants are shown in Table 3.

Methods used to assess scarring

All five burn wound studies[22–26] evaluated scarring using the Vancouver Scar Scale (VSS) (Table 4). There was variability in how the studies operationalized the VSS to determine hypertrophic scarring. Two studies employed a dichotomous outcome based on total VSS score (<7).[24,25] The other studies[22,23,26] used one or more subscales of the VSS separately and these were treated as continuous measures in the analyses (pigmentation was dichotomized in one study[22]). Three studies reported details of the scar scale assessor, as either research nurses[24,25] or study investigators[22] and two studies[23,26] did not report who performed the assessment. The median time of final scar assessment ranged from 6.4 to 10.4 months.

Further details of the methods used to assess scarring are reported in Table 4.

Two of the surgical wound studies assessed scarring using the VSS,[29,30] another used the patient and observer scar assessment scale (POSAS) and Scar Cosmesis Assessment and Rating (SCAR) Scale,[28] and the fourth study[27] did not use a rating scale, instead classifying scars as normal, hypertrophic, or keloid based on defined clinical features (time since surgery and physical appearance of the scar). There was variability

Table 2. *Characteristics of included studies*

	Sood et al. (2015)[24]	*Sood* et al. (2015)[23]	*Sood* et al. (2016)[22]	*Thompson* et al. (2013)[25]	*Wallace* et al. (2019)[26]	*Gao* et al. (2014)[27]	*Ilies* et al. (2019)[28]	*Kulawczuk* et al. (2014)[29]	*Ward* et al. (2012)[30]
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Nested case–control	Case–control	Cohort
Country	United States of America	United States of America	United States of America	United States of America	Australia and United Kingdom	China	Romania	Poland	Australia
Dates	2007–2014	2007–2013	2007–2014	—	—	—	—	2009–2012	2007–2008
Number of centers	Single	Single	Single	—	Multicenter	Single	Single	Single	Multicenter
Study type	Candidate gene association	GWAS	Candidate gene association	Candidate gene association	EWAS	Candidate gene association	Candidate gene association	Candidate gene association	Candidate gene association
Polymorphism(s) investigated	8 MC1R SNPs	Genome wide	2,146 MAPK-pathway SNPs	rs36228499 in the p27kip1 gene	Exome wide	p53 codon-72 SNPs	Null alleles of the isoforms GSTT1 and GSTM1	C(–509)T in the promoter region of the TGF-β1 gene (rs1800469)	rs8110090 in TGF-β1
Population	Burns	Burns	Burns	Burns	Burns	Surgical wounds	Surgical wounds	Surgical wounds	Surgical wounds
Inclusion criteria	Adults ≥18 with DPT burns or delayed healing ≥2 weeks	Adults ≥18 with DPT burns or delayed healing ≥2 weeks	Adults ≥18 with DPT burns or delayed healing ≥2 weeks	Adults ≥18 at risk of HTS due to depth and healing time	Adult/child hospital admission, outpatient treatment, or HTS treatment	Cesarean section	Adult >18 cesarean section with no complications	Cardiac surgery	WA Melanoma Health (population-based) Study participants, adult ≥18 with invasive cutaneous melanoma[50]
Exclusion criteria	—	—	—	—	>1 acute burn history, treated outside WA, previous keloid	Pathological scar or tumors	Unable to follow up, incision overlaps previous surgery or trauma	—	—
Setting	Burns center	Burns center	Burns center	—	Outpatient clinics, burn wards	Hospital	Gynecology clinic	—	—
Outcome assessed	HTS	HTS	HTS	HTS	HTS	HTS, keloids	HTS	Keloids	HTS
Length of follow-up	≥6 months	6–12 months	6–12 months[a]	6–12 months	3, 6, 12 months	12–18 months	6 months	—[b]	≥6 months
Sample size calculation?	Yes	Yes	No	Yes (*post-hoc*)	Yes	No	No	No	No
Adequately powered?	Yes	Yes	—	Yes	Yes	—	—	—	—

[a]Participants were those included in Sood *et al.* (2015).[23] Length of follow-up taken from this article.
[b]Participants underwent surgery between 2009 and 2010. Inferred from publication date that at least 6 months had elapsed.
DPT, deep partial thickness; EWAS, exome-wide association study; GWAS, genome-wide association study; HTS, hypertrophic scarring; SNP, single nucleotide polymorphism; WA, Western Australia.

Table 3. *Characteristics of participants in included studies*

	Sood et al. *(2015)*[24]	*Sood* et al. *(2015)*[23]	*Sood* et al. *(2016)*[22]	*Thompson* et al. *(2013)*[25]	*Wallace* et al. *(2019)*[26]	*Gao* et al. *(2014)*[27]	*Ilies* et al. *(2019)*[28]	*Kulawczuk* et al. *(2014)*[29]	*Ward* et al. *(2012)*[30]
No. included in analyses/ enrolled in study	425/568	538/638	538/638	300/unclear	665/953	260/260	54/72	73/100	202/874
Age (years)	Median 40 (IQR 28–52)	Median 40 (IQR 28–53)	Median 40 (IQR 28–53)	Median 39 (range 18–91)	Median 27.9 (IQR 15.6–46.7)	Mean 29.4 (range 20 and 39 years)	Mean 30.92 (SD 5.11)	Mean 64.75 (SD 9.37)	Mean 60 (range 27–81)
Male/Female	298/217	382/156	382/156	206/94	440/225	0/260	0/72	51/22	103/99
Race	White 327 (79%), Asian 23 (6%), Black/African American 15 (4%). Native American 9 (2%), other/multiple 39 (9%). Not available for 13 participants	White 408 (76%), Asian 26 (5%), Black/ African American 19 (4%), Native American 11 (2%), other/multiple 57 (11%). Not available for 17 participants	White 408 (76%), Asian 26 (5%), Black/ African American 19 (4%), Native American 11 (2%), Other/multiple 57 (11%). Not available for 17 participants	White 235 (79%), American Indian/ Alaskan Native 9 (3%), Asian 19 (6%) Black/ African American 11 (3.7%), Native Hawaiian/Pacific Islander 1 (0.3%), Hispanic 24 (8%)	All included in the analysis were of European descent. Fitzpatrick skin type: 1 ($n=15$), 2 ($n=219$), 3 ($n=349$), 4 ($n=65$), 5 ($n=6$), 6 ($n=1$)	Not reported, assumed to be 100% Chinese/ Asian	Not reported	Not reported	Not reported
Wound details	Burn size (% TBSA) median 7 (IQR 3–15) Burn mechanism and anatomical region not reported	Burn size (% TBSA) median 6 (IQR 2–14) Burn mechanism and anatomical region not reported	Burn size (% TBSA) median 6 (IQR 2–14) Burn mechanism and anatomical region not reported	Burn size (% TBSA): median (range) 7.1 (0.25–80). TBSA <20% ($n=230$), TBSA ≥20% ($n=69$). Anatomical region: Face ($n=8$), Torso ($n=48$), Upper extremity ($n=108$), Lower extremity ($n=103$). Burn mechanism not reported	TBSA not reported Mechanism: Flame ($n=280$), Contact ($n=140$), Scald ($n=196$), Sunburn or radiation ($n=4$), Chemical ($n=29$), Friction ($n=13$), Electrical ($n=3$). Anatomical region: Face/ head/neck ($n=22$), Chest/abdomen/groin ($n=74$), Back/buttocks ($n=31$), Arm ($n=185$), Hand ($n=61$), Leg ($n=236$), Foot ($n=52$), Genitalia ($n=1$).	Cesarean section (transverse incision $n=249$, longitudinal incision $n=11$)	Cesarean section	Cardiac surgery	Time since excision (months): Mean 13 Range 6–40 Excision site: Head and neck 20 (10%), trunk 80 (39%), upper limb 60 (30%), lower limb 42 (21%)
Treatments received	64% required at least one operation	63% required at least one operation	63% required at least one operation	Not reported	Reconstructive surgery ($n=107$), >1 surgical procedure ($n=108$). Text suggests some patients were treated with reconstructive surgery, intralesional steroids, or laser therapy but numbers not reported	Not reported	Not reported	Not reported	Not reported

(*continued*)

Table 3. (*Continued*)

	Sood et al. *(2015)*[24]	*Sood* et al. *(2015)*[23]	*Sood* et al. *(2016)*[22]	*Thompson* et al. *(2013)*[25]	*Wallace* et al. *(2019)*[26]	*Gao* et al. *(2014)*[27]	*Ilies* et al. *(2019)*[28]	*Kulawczuk* et al. *(2014)*[29]	*Ward* et al. *(2012)*[30]
No. with hypertrophic/ keloid scarring	Severe hypertrophic scarring: 208 Normal/not severe scarring: 217	N/A (dichotomous measure of scarring not reported in the study)	N/A (dichotomous measure of scarring not reported in the study)	Hypertrophic scarring: 126 Normal scarring: 174	N/A (dichotomous measure of scarring not reported in the study)	Hypertrophic scarring: 22 Keloid scarring: 0 Normal scarring: 238	Hypertrophic scarring: 13 Normal scarring: 54 (5 patients developed atrophic scarring).	Keloid scarring: 50 Normal scarring: 50	N/A (dichotomous measure of scarring not reported in the study)
Missing data	Blood sample not provided or outcome data not available for 143 patients Racial distribution of subjects who were not genotyped or had incomplete clinical follow-up did not differ significantly from that of the 425 subjects included in the analysis	25 participants lost to follow-up before providing blood sample or having a scar assessment. Fifteen subjects had genotypic data that did not pass quality control, 60 were either lost to follow-up or had not yet had a scar assessment at the time of analysis	25 participants lost to follow-up before providing blood sample or having a scar assessment. Fifteen subjects had genotypic data that did not pass quality control, 60 were either lost to follow-up or had not yet had a scar assessment at the time of analysis	Not reported	283 participants were removed for the following reasons: failed genotyping ($n=32$); low call rate (<95%)($n=6$); sex-ambiguous ($n=6$); consent incomplete ($n=2$); Keloid scar or history of keloid scar ($n=25$); missing demographic or clinical information ($n=7$); missing scar outcome data ($n=51$);relatedness >0.125 ($n=4$); non-CEU (non-European) ancestry($n=150$).	No missing data	No missing data	DNA could not be isolated in 27 patients	During the study period, 265 (30%) of 874 participants attended the clinic for scar assessment and provided a blood sample for DNA extraction. Thirty-eight (14%) of these 265 participants excluded due to having received a skin graft, 25 cases (9%) with scars <6 months old were excluded

IQR, interquartile range; N/A, not applicable; SD, standard deviation; TBSA, total burn surface area.

Table 4. *Details of scarring outcome assessment*

	Sood et al. *(2015)*[24]	*Sood* et al. *(2015)*[23]	*Sood* et al. *(2016)*[22]	*Thompson* et al. *(2013)*[25]	*Wallace* et al. *(2019)*[26]	*Gao* et al. *(2014)*[27]	*Ilies* et al. *(2019)*[28]	*Kulawczuk* et al. *(2014)*[29]	*Ward* et al. *(2012)*[30]
Outcome	Severe hypertrophic scarring; Itch severity	Scar height	Pigmentation; vascularity; pliability; height	Hypertrophic scarring; clinically significant itch	Scar height; scar pliability	Keloid scarring; hypertrophic scarring	Hypertrophic scarring	Keloid scarring	Primary scar outcome (combination score reflecting vascularity, height, and pliability); secondary scar outcome (combination score reflecting vascularity, height, pliability, and pigmentation
Data type	Dichotomous (severe hypertrophic scarring); continuous (itch severity)	Continuous	Dichotomous (pigmentation); continuous (Vascularity, pliability, and height)	Dichotomous	Continuous	Dichotomous	Dichotomous	Dichotomous	Continuous
Name of scale	VSS; Self-reported rating of scar-associated itch on scale of 0–10 (0 = no itch)	VSS height subscale (0–3)	VSS. Vascularity (0–3), pliability (0–5), height (0–3), pigmentation (0–2)	VSS; self-reported rating of scar-associated itch on scale of 0–10 (0 = no itch)	Modified VSS. Height (0–4) and scar pliability (0–5)	None	SCAR and POSAS	VSS	VSS
Cutoff	Severe hypertrophic scarring >7	N/A	Pigmentation subscale ≥1	Hypertrophic scarring >7. Clinically significant itch >4	N/A	N/A	Not reported	≥9 (keloids); ≤3 (healthy scar)	N/A
Timing of scarring assessment (months)	Median 7 (range 3–20)	Median 6.4 (IQR 3.7–7.7)	Median 6.4 (IQR 3.7–7.7)	Participants seen at two follow-up visits (1–5 months and 6–12 months postinjury). The highest VSS and itch scores of the two follow-up assessments used for analysis	Median 10.40 (IQR 5.80–13.95)	Range 12–18 months	Scars evaluated at 3 and 6 months. Not clear which timepoint the analyses are based on	Not reported[a]	Mean 13 (range 6–40)
Assessor	Research nurse	Not reported	One of the study authors (Shari Honari)	Research nurse	Not reported	Not reported	Study investigator	Not reported	"Trained examiners"
Scarring assessed the same way for all patients?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Blind assessment?	Not reported	Not reported	Not reported	Yes	Not reported	Unclear	Not reported	Unclear	Not reported

(*continued*)

Table 4. (*Continued*)

	Sood et al. *(2015)*[24]	*Sood* et al. *(2015)*[23]	*Sood* et al. *(2016)*[22]	*Thompson* et al. *(2013)*[25]	*Wallace* et al. *(2019)*[26]	*Gao* et al. *(2014)*[27]	*Ilies* et al. *(2019)*[28]	*Kulawczuk* et al. *(2014)*[29]	*Ward* et al. *(2012)*[30]
Other methods used to assess scarring	None	None	None	None	None	Scar assessment based on clinical features and categorized as keloid, hypertrophic, or normal	Patient-submitted photos	None	None
Other (nongenetic) prognostic factors included in the model	None	Age, sex, percent total body surface area (% TBSA) burned, number of operations	Age, sex, percent total body surface area (% TBSA) burned, number of operations	Age, sex, race/ethnicity, percent total body surface area (% TBSA) burned, burn location	Age at time of injury, sex, number of surgical procedures, % total body surface area (% TBSA) of the burn	None	Age, weight, and BMI	None	Length and width of the scar (mm), age at time of examination (years), scar site, body mass index; self-reported skin color; tendency to burn (based on the Fitzpatrick scale); medical conditions related to immune response or inflammation that were hypothesized to affect scar outcome; wound or systemic infection at the time of melanoma removal; and scar management techniques (use vs. nonuse).

[a]Participants underwent surgery between 2009 and 2010. Inferred from publication date that at least 6 months had elapsed.
BMI, body mass index; POSAS, Patient and Observer Scar Assessment Scale[35]; SCAR, Scar Cosmesis Assessment and Rating scale[51]; VSS, Vancouver Scar Scale.[34]

in how the included studies operationalized the scales to determine scarring.

Two of the surgical wound studies reported details of who conducted the assessment (study investigators or "trained examiners").[28,30] Length of follow-up was 6 months in one study,[28] 12–18 months in a second,[27] a mean of 13 months in the third study,[30] and unclear in the final study.[29] Further details in Table 4.

Missing data

One burn wound study reported no missing data.[25] The percentage of participants that could not be included in the analyses due to missing data across the other four studies ranged from 15.7% to 25.2%.

Two surgical wound studies reported no missing data.[27,28] The percentage of participants that could not be included in the analyses due to missing data in the other two studies was 27%[29] and 77%.[30] Further details are reported in Table 3.

Comparison of studies of burns patients and other types of wounds

The sample sizes of the studies of burns patients (median 638 IQR 501–717)[22–26] were larger than those for studies of surgical wounds (median 180, IQR 79–721),[27–30] but this difference was not statistically significant (Mann–Whitney U, $p = 0.14$). Where studies reported a dichotomous outcome (*i.e.*, presence or absence) of hypertrophic or keloid scarring, a much higher percentage of participants in the burns' studies developed these forms of scarring than in the studies of other types of wound (46.1% vs. 10.7%, $\chi^2 = 123.7$, $p < 0.001$[24,25,27–29]).

Length of follow-up was shorter in most of the burns' studies than length of follow-up in studies of surgical wounds, although there was some overlap between studies (between 3 and 12 months in the burns' studies, and 6 and 18 months, where reported, in the surgical studies).

DISCUSSION

This scoping review aimed to summarize the methodology used in studies of genetic associations with the development of keloid or hypertrophic scarring after acute wound injury in adults and children. We identified a small body of evidence in burns patients and those with surgical wounds. No studies of other types of wounds (*e.g.*, trauma) were identified. Most studies looked at the association between genetic variants and hypertrophic scarring rather than keloid outcomes. Only one study clearly reported that all participants had been followed up for at least a year. More than three quarters of included participants were white in five of the six studies that reported information about race.

Seven of the nine studies included in this review used a prospective cohort design (participants were recruited at the time of wounding and followed up over time to determine the incidence of hypertrophic or keloid scarring). Case–control studies are common in genetic association research[31] as they are faster and less costly to conduct than cohort studies (in a case–control study, participants are recruited based on outcome status and exposure is retrospectively determined).[32] However, case–control studies can be biased if the controls are not selected from the same population as the cases and have therefore not had the same potential to be diagnosed as a case.[31]

The retrospective nature of data collection in case–control studies can also be a source of bias. In studies of genetic association, the presence or absence of genetic variants can be reliably assessed retrospectively, but other characteristics of participants that may affect the outcome (*e.g.*, treatment received) can be subject to recall bias, inaccurate recording, or inconsistent measurement between participants.[33] Cohort studies follow up participants selected from one population and, if prospectively designed, the investigator has complete control over the data that are collected on participants.[33] Thus they can avoid the biases inherent in case–control studies.

Many of the included studies did not report a sample size calculation. Lack of statistical power is a common problem in genetics research.[34] Most genes contributing to complex disorders are associated with only a very modest increase in disease risk, and so large samples are needed to detect these with sufficient power.[35] It is important therefore that researchers estimate the required sample size when planning their study using appropriate methods.[36]

All of the studies relied on subjective methods to assess scarring (based on observer or patient opinion). Objective measurement tools such as imaging devices have been developed but studies to evaluate their accuracy and reliability are scarce.[37] Most studies used rating scales, such as the VSS[38] and POSAS,[39] to determine scarring, but there was considerable heterogeneity in how scales were operationalized.

Comparability of studies would be increased by using the same outcome definition and measurement sale.[40] However, there is currently no consensus on which scar scale is best,[41] what score on a scale constitutes clinically relevant hypertrophic or keloid scarring,[42] or even how hypertrophic and keloid scarring are defined.[43] Most scar scales rely on clinicians' judgment rather than the patients' opinion. Consequently, their focus is on a relatively narrow range of features that do not incorporate patient-observed issues such as pain and itch[41] and

the cosmetic, functional, and psychological sequalae of scarring.[44]

Scar quality is affected by length of follow-up, which was short in many studies, particularly in those involving burns patients. Improvements in scar quality have been observed in the 12–36 months following both burns[45] and incisional scars.[46] A shorter length of follow-up may therefore have resulted in the misclassification of scarring in some included studies.

This scoping review has established several gaps in the literature. First, no studies were identified involving patients with acute wounds due to trauma. Second, very few studies of keloid scarring were identified. Finally, the majority of participants in the included studies were white/Caucasian, which may limit the generalizability of their findings to other ethnic groups. Epigenetic and environmental factors may also play a role in the development of hypertrophic or keloid scarring.[47] These were not the focus of this review.

Some potential limitations of our review should be acknowledged. First, the review was limited to English language publications for pragmatic reasons. Conference abstracts were also excluded as these would not have contained sufficient information about study methodology. It is possible therefore that a complete set of studies was not identified. Second, only 15% of references were screened by two reviewers. However, interrater reliability for the dual screened references was high, indicating a strong degree of confidence in the selection process.

Finally, our review was hampered by the quality of reporting in the included studies, many of which did not report details such as numbers eligible, detailed inclusion and exclusion criteria, power calculations, or treatments received by participants to reduce or prevent scarring. It is important that studies are reported fully and transparently. It is recommended that researchers consult the STrengthening the REporting of Genetic Association Studies (STREGA) guidelines[48] for the reporting of genetic association studies when publishing their studies.

TAKE-HOME MESSAGES

- An increased understanding of who is at risk of developing hypertrophic or keloid scarring will facilitate personalized medicine, where scar prevention measures can be targeted at those patients who need them most.
- A small body of evidence exists on the association between genetic variants and hypertrophic or keloid scarring following acute wounding.
- All studies have been conducted in patients who have experienced burns or surgical wounds and mostly of hypertrophic scarring.
- Sample sizes were small, participants were mostly white/Caucasian, and length of follow-up was often too short to allow adequate scar maturation.
- It is recommended that future research uses a prospective cohort design, recruiting large samples of participants from ethnically diverse populations and following up participants for at least 12 months.
- Further research and consensus on how to define and measure scar severity is needed.

SUMMARY

This article reports the findings of a scoping review of the methodology used in studies of genetic influences on the development of keloid or hypertrophic scarring in adults and children. A small body of evidence was identified in burns and surgical patients, and mostly relating to hypertrophic scarring.

Further studies are needed, especially of keloid scarring, and in a wider range of populations, including patients with wounds caused by trauma. Future studies should recruit large and ethnically diverse populations and follow up participants for at least 12–36 months to allow for adequate scar maturation.[41,42] The methodological literature supports the use of a prospective cohort design to reduce the risk of bias in the findings.[32,33] Further research to achieve consensus on how scar quality should be defined and measured is also needed.[44,49]

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SUPPLEMENTARY MATERIAL

Supplementary Appendix S1

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Abbreviations and Acronyms

BIOSIS = Biosciences Information Service
BMI = body mass index
DPT = deep partial thickness
EMBASE = Excerpta Medica Database
EWAS = exome-wide association study
GWAS = genome-wide association study
HTS = hypertrophic scarring
HuGE = Human Genetic Epidemiology
IQR = interquartile range
POSAS = Patient and Observer Scar Assessment Scale
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO = Prospective Register of Systematic Reviews
SCAR = Scar Cosmesis and Assessment Rating
SD = standard deviation
SNP = single nucleotide polymorphism
STREGA = STrengthening the REporting of Genetic Association Studies
TBSA = total burn surface area
VSS = Vancouver Scar Scale