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Research article

Exploring somatosensory innervation of the human lip: A focus on the vermilion

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A R T I C L E I N F O

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A B S T R A C T

Background: The lips are a vital component of the face and are densely innervated to perform various functions. The lip edges are covered with mucocutaneous tissue called vermilion which is particularly receptive to touch and temperature. The aim of this study was to investigate the somatosensory innervation of human lips, focusing on sensory corpuscles and the presence of mechano-gated (ASIC2, PIEZO2, and TRPV4) and thermosensing (TRPV1, TRPM2, and RPM8) ion channels within them.

Methods: Twelve intact lips (6 upper and 6 lower) were obtained from non-embalmed frozen cadavers (five females and seven males) with an age range of 60–80 years. The specimens were divided into three zones (medial, lateral, and median). The morphotypes of sensory corpuscles and their immunohistochemical profile was analysed. The occurrence of ion channels involved in mechanosensation and temperature detection was examined using various antibodies. Sensory corpuscle density was quantified in vermilion sections, and statistical analyses were conducted to assess differences between the upper and lower lips, as well as between females and males ($p < 0.05$).

Results: Different morphotypes of sensory corpuscles were identified: Ruffini-like associated with hair follicles, Meissner and glomerular corpuscles in the vermilion, and less classifiable sensory corpuscles within the mucosa. The density of sensory corpuscles in the vermilion was higher in the upper lip than in the lower lip; glomerular corpuscles predominated in the medial and median segments, whereas Meissner corpuscles were more abundant in the lateral segment. No sex-related differences were observed in the density or distribution of the two main corpuscular morphotypes. In contrast, the axons of both the glomeruli and Meissner corpuscles regularly displayed ASIC2 and PIEZO2 immunoreactivity, whereas immunoreactivity for TRPV1, TRPV4, TRPM2, and TRPV8 was absent.

Conclusions: These results demonstrate that the sensory corpuscles of the vermilion are a mixture of those typical of glabrous skin mucocutaneous tissues. The presence of PIEZO2 and ASIC2 in their axons suggests that these sensory corpuscles function as mechanosensors.

1. Introduction

The lips are a vital component of the human face, serving various functions such as facial expression, mastication, speech and phonation, touch and thermal sensation, physical attractiveness, and aspects of sexuality. Anatomically, these bilateral cutaneous-mucous folds contain an intrinsic network of muscles, vessels, and nerves (Shim et al., 2008; Hur et al., 2010; Piccinin and Zito, 2022). The external lip surface is covered with hairy skin, housing abundant sweat and sebaceous glands, while the internal surface is covered with a moist mucous membrane. The lip edges are covered with mucocutaneous tissue called vermilion (see Boukovalas et al., 2017). The lips are densely innervated to perform

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Table 1
Primary antibodies used in this study.

Antigen	Origin	Dilution	Supplier
ASIC2	Rabbit	1:200	LifeSpan BioSciences[1]
CD34 (clone QB-END/10)	Mouse	Prediluted	Master Diagnostica[2]
Glut1	Rabbit	0.5 μg/ml	Cell Marque[3]
NSE (clone BBS/NC/VI-H14)	Mouse	1:1000	Dako[4]
NFP (clone 2F11)	Mouse	1:100	Dako[4]
PIEZO2	Rabbit	1:200	Sigma-Aldrich[5]
S100 protein (clone 4C4.9)	Mouse	1:1000	ThermoFisher Scientific[6]
S100 protein	Rabbit	1:1000	Dako[4]
TRPM2	Rabbit	1:100	ThermoFisher Scientific[6]
TRPM8	Rabbit	1:200	Sigma-Aldrich[5]
TRPV1	Rabbit	1:200	Sigma-Aldrich[5]
TRPV4	Rabbit	1:200	LifeSpan BioSciences[1]

Glut1: glucose transporter 1; NSE, neuron-specific enolase; NFP, neurofilament protein
[1]Seattle, WA; [2]Granada, Spain; [3]Seattle, WA, USA; [4]Glostrup, Denmark; [5]Saint Louis, MS, USA; [6]Freemont, CA, USA.

various function. The facial nerve governs motor innervation of the labial muscles, whereas somatosensory innervation depends on the branches of the trigeminal nerve (Alsaad et al., 2003; Hwang et al., 2004, 2007; Hu et al., 2006, 2007a, 2007b).

Somatosensory innervation of the lips has been widely investigated in different mammalian species such as mice (Yamamoto and Sakada, 1981), rats (Yamamoto et al., 1986; Tachibana et al., 1987b; Watanabe et al., 2013), cats, miniature pigs (Tachibana et al., 1989), dogs (Tachibana et al., 1987a), *Monodelphis domestica* (Schulze et al., 1993), and *Cebus apella* monkeys (Iyomasa et al., 1978). Across these species, distinct morphological variations of sensory corpuscles have been identified (Watanabe, 2004). However, insights into human somatosensory innervation remains limited. A seminal study by Seto (1963) from six decades ago remains a primary reference, describing various structures including "complex branched sensory terminations", "uncapsulated glomerular bodies", "capsulated glomerular terminations (genital nerve body type I)", and "plexiform sensory terminations". More recently, Nolano et al. (2013) observed abundant intraepithelial nerve fibres, pilo-neural complexes comprising unmyelinated and myelinated fibres, Merkel cell-neurite complexes, Ruffini-like corpuscles, and occasionally Meissner-like corpuscles in 2-mm punch labial biopsies.

In contrast, results from microneurography studies provide evidence for distinct categories of low threshold mechanoreceptive afferents (LTMRs) innervating the lips, including type I and type II slowly adapting (SA) LTMRs, and type I rapidly adapting (RA) LTMRs. However, type II RA LTMRs have not been reported (Trulsson and Johansson, 2002; Bukowska et al., 2010; Trulsson and Essick, 2010). In vertebrate skin, these LTMRs are associated with Merkel cell-neurite complexes, Ruffinís corpuscles, and Meissner corpuscles (Zimmerman et al., 2014; Cobo et al., 2021).

Thus, the aim of this study was to investigate the somatosensory innervation of the human lips by analysing the morphotypes of sensory corpuscles, their immunohistochemical profile (using a battery of antibodies against the different constituents of the sensory corpuscles; see Cobo et al., 2021), the occurrence of ion channels involved in mechanosensation (PIEZO2, acid-sensing ion channel 2 -ASIC2- and transient receptor potential vanilloid 4 -TRPV4-), and temperature detection (transient receptor potential melastatina 2 and 8 -TRPM2 and TRPM8- or TRPV1) (Martín-Alguacil et al., 2021).

2. Material and methods

2.1. Material and tissue processing

This study was approved by the Ethics Committee for Biomedical Research of the Principality of Asturias, Spain (Cod. CElm, PAst: Proyecto 266/18). Upper (n = 6) and lower (n = 6) human lips were obtained from our laboratory's repository (Registro Nacional de Biobancos, Sección Colecciones, Ref. C-0001627). The specimens were originally obtained from non-embalmed frozen cadavers, including five

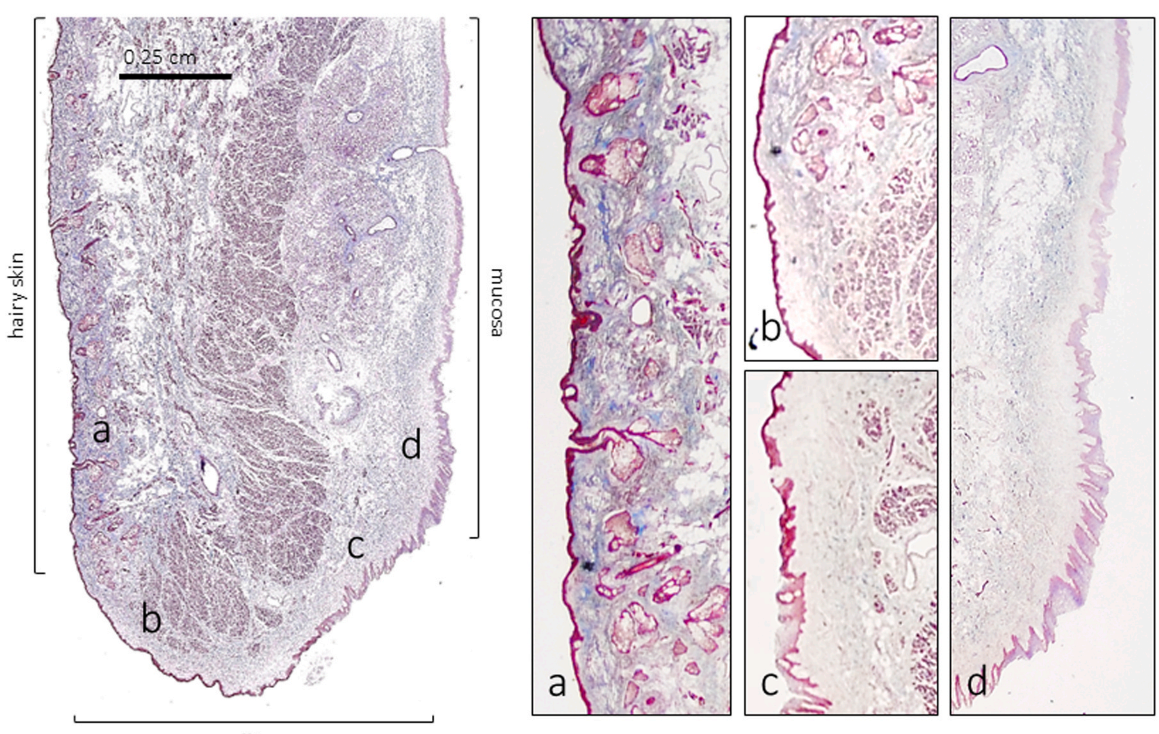

Fig. 1. Cross-section of a human upper lip (left) showing the skin (a), external (b) and internal (c) parts of the vermilion, and the mucosa (d). The tissues were stained with Masson's trichrome.

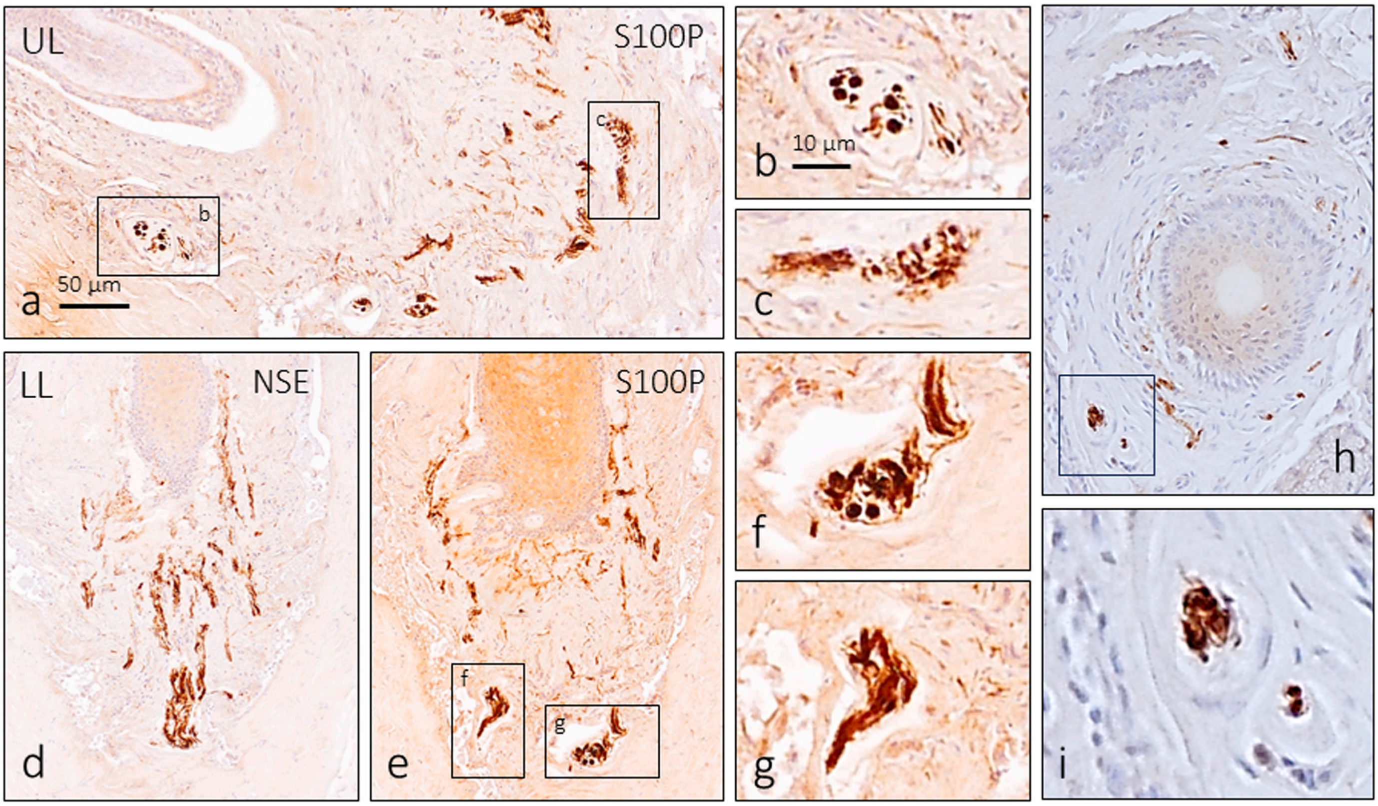

Fig. 2. Innervation of the dermal papilla and peripapillary dermis. Isolated nerve fibres (d and e) and sensory corpuscles (a, e, and h) corresponding to Ruffini-like corpuscles are associated with the hairy papilla. Enlargements (b, c, f, and g) are shown from the squares in a, e, and h. UL: upper lip; LL: lower lip.

Table 2
Density of sensory corpuscles in the human lips/mm^2.

			Medial zone	Median zone	Lateral zone
Upper lip	**Female**	**MC**	4,28 ± 0,88	4,02 ± 1,01	4,32 ± 0,91
		GC	5,21 ± 1,43	5,27 ± 1,12	3,90 ± 0,97
		RC	2,20 ± 0,30	2,22 ± 0,41	2,39 ± 0,81
	Male	**MC**	3,86 ± 1,00	3,98 ± 0,93	4,61 ± 1,14
		GC	5,22 ± 2,01	5,31 ± 1,02	3,52 ± 0,95
		RC	4,80 ± 1,44	5,03 ± 1,25	4,60 ± 0,93
Lower lip	**Female**	**MC**	3,71 ± 0,77	3,93 ± 0,86	4,11 ± 0,95
		GC	4,44 ± 1,23	4,26 ± 0,94	3,82 ± 0,86
		RC	2,04 ± 0,20	1,96 ± 0,13	2,22 ± 0,46
	Male	**MC**	3,94 ± 0,99	3,96 ± 0,89	4,40 ± 0,95
		GP	4,82 ± 1,04	4,62 ± 1,11	3,28 ± 0,77
		RC	2,89 ± 0,48	3,51 ± 1,36	3,90 ± 0,64

MC: Meissner corpuscles; GC: glomerular corpuscles. Results for Ruffini-like corpuscles (RC) are expressed as number of corpuscles by hair papilla.

females (three upper lips and two lower lips) and seven males (three upper lips and five lower lips), with ages ranging from 60 to 81 years. Subsequently, the lips were divided into three zones: medial (between both philtrum ridges on the upper lip and a central 2 cm segment on the lower lip), lateral (2 cm medial to the oral commissure), and median (1 cm space between the medial and lateral zones). After fixation in 10% formaldehyde, the samples were preserved in paraffin for later use. Serial sections of 10 µm thickness were prepared from the tissue blocks and randomly selected sections were stained with Masson's trichrome to delineate structural characteristics. The antigenicity of the stored sections was evaluated across 10 randomly selected sections, revealing no discernible differences compared with the newly processed sections.

2.2. Immunohistochemistry

De-paraffinised and rehydrated sections were processed for indirect immunohistochemistry using a Leica Bond Polymer Refine Detection Kit (Leica Biosystems™, Newcastle, UK) following the manufacturer's instructions. The primary antibodies used are listed in Table 1. These included specific markers for axons (neuron-specific enolase [NSE]), Schwann and terminal glial cells (S100 protein: S100P), endoneurium (CD34 antigen), and perineurium (Glucose transporter 1, Glut1). Furthermore, we used antibodies against PIEZO2, ASIC2, TRPV4, TRPV1, TRPM2, and TRPM8 ion-channel-specific epitopes. Indirect immunohistochemistry included negative and positive controls, as well as internal positive and negative controls.

2.3. Quantitative analyses

The density of sensory corpuscles within the vermilion was quantified by analysing five sections in each pre-established zone. These sections were separated from each other by 200 µm, and processes for S100P detection. Upon visualising the immunoreaction and mounting the coverslip, the sections were scanned using the SCN400F scanner (Leica Biosystems™) and digitally processed using the SlidePath Gateway LAN programme (Leica Biosystems™). Subsequently, on 4 × 500 µm magnified images, a grid of 4 mm^2 was randomly applied to five non-overlapping vermilion fields, adjusting the grid to the surface (20 mm^2 per section; 100 mm^2 per zone). The sensory corpuscles within the grid were counted by two independent observers (JM-C and JAV), and the results obtained were averaged. Data are expressed as mean ± standard deviation (SD)/mm^2. Normal distribution was assessed using the Kolmogorov–Smirnov test. A *t*-test was used for paired data and analysis of variance (ANOVA) was used for repeated measurements to assess differences between the upper and lower lips, as well as between females and males. Statistical significance was set at $p < 0.05$.

Furthermore, within the same sections, the corpuscles associated with the papilla and peripapillary dermis were counted in five hair follicles per section. Data are expressed as mean ± SD/hairy papillae.

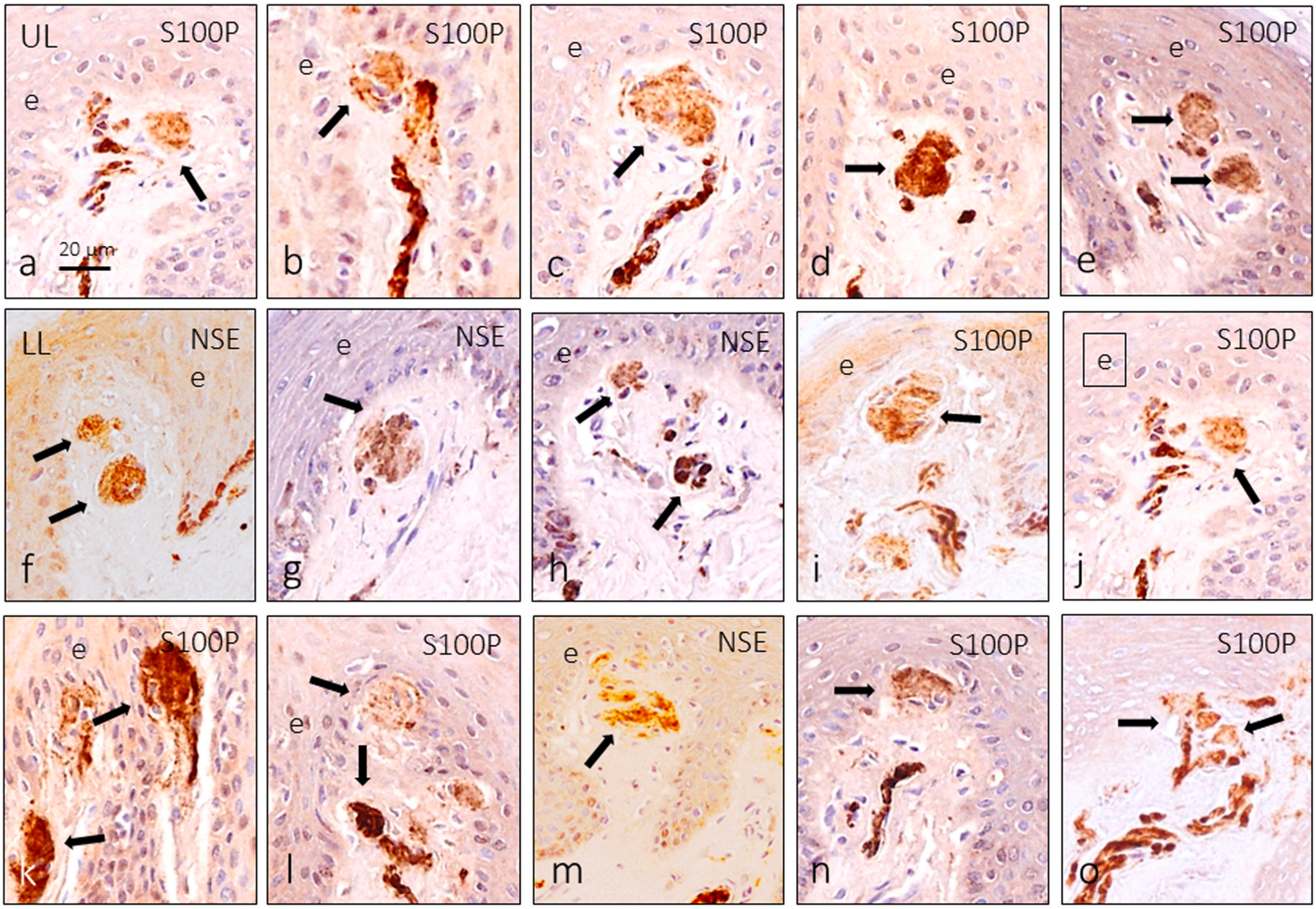

Fig. 3. Meissner corpuscles in the vermilion. Meissner corpuscles were observed within the dermal papillae of the vermilion. e: epidermis; UL: upper lip; LL: lower lip.

Owing to the irregularities observed in the papillae across sections, these results were not subjected to statistical analysis.

3. Results

To systematically investigate the innervation of the human lips, we defined three distinct territories: cutaneous, mucous, and the transitional region between them (the vermilion) (Fig. 1).

3.1. Hairy skin

The study of nerve structures of hair bulbs was constrained owing to significant alterations of the outer and perifollicular sheaths caused by plucking, freezing, and fixation processes. Therefore, only the innervation of the hair papillae and the surrounding associated dermis are described here. Nerve fibres entering the papillae were regularly observed, and isolated nerve profiles and sensory corpuscles were found in the peripapillary dermis (Fig. 2), most of which were identifiable as Ruffini-like corpuscles. The highest density of sensory nerve formation associated with hair papillae was observed in the median zone of the lips, followed by the lateral and medial zones (Table 2).

3.2. Vermilion

Two predominant morphotypes of sensitive corpuscles were found in the mucocutaneous tissue of the vermilion: Meisner's corpuscles (Figs. 3 and 4) and the glomerular corpuscles (Fig. 5).

Meissner corpuscles were located within dermal papillae, at varying distances from the epidermis. These corpuscles exhibited diverse sizes and morphologies, and the laminar cells (terminal glial cells) were not compact nor arranged as stacks of flattened sheets (classically described as a "coin stack"). The immunoreactivity of S100P was not homogeneous between corpuscles or within the same corpuscle, with immunostaining intensity weaker in lamellar cells than in Schwann cells of the nerve fibres that supply them (Fig. 3). The axons exhibited a distinctive glomerular and pointed appearance rather than the typical lamellar cell appearance(Fig. 3). Meissner corpuscles were surrounded by a complete or partial layer of CD34-positive cells, forming a capsule continuous with the endoneurium of the nerve trunks (Fig. 4). Conversely, no pericorpuscular immunoreactivity for Glut-1, indicative of perineurium, was observed (data not shown).

Regarding the glomerular corpuscles (Fig. 5), they exhibited a "wool ball" or "yarn ball" appearance, consistently located beneath the basal epithelial layer of the vermilion. The distribution patterns of S100P and NFP or NSE were irregular, suggesting a complex arrangement of axons and terminal glial cells within the glomerular corpuscles (Fig. 5). Notably, CD34-positive and/or Glut-1 positive capsules surrounding glomerular corpuscles were absent in all cases (data not shown).

The results of the quantitative analysis of Meissner and glomerular corpuscle densities in the vermilion, along with the Ruffini-like corpuscles associated with hair follicles, are summarised in Table 2. Typically, the glomerular corpuscle density was higher than that of Meissner corpuscles in the medial and median lip segments and was lower in the lateral segment. Furthermore, the density of corpuscles was higher in the upper lip than in the lower lip, and no sex-related differences were observed.

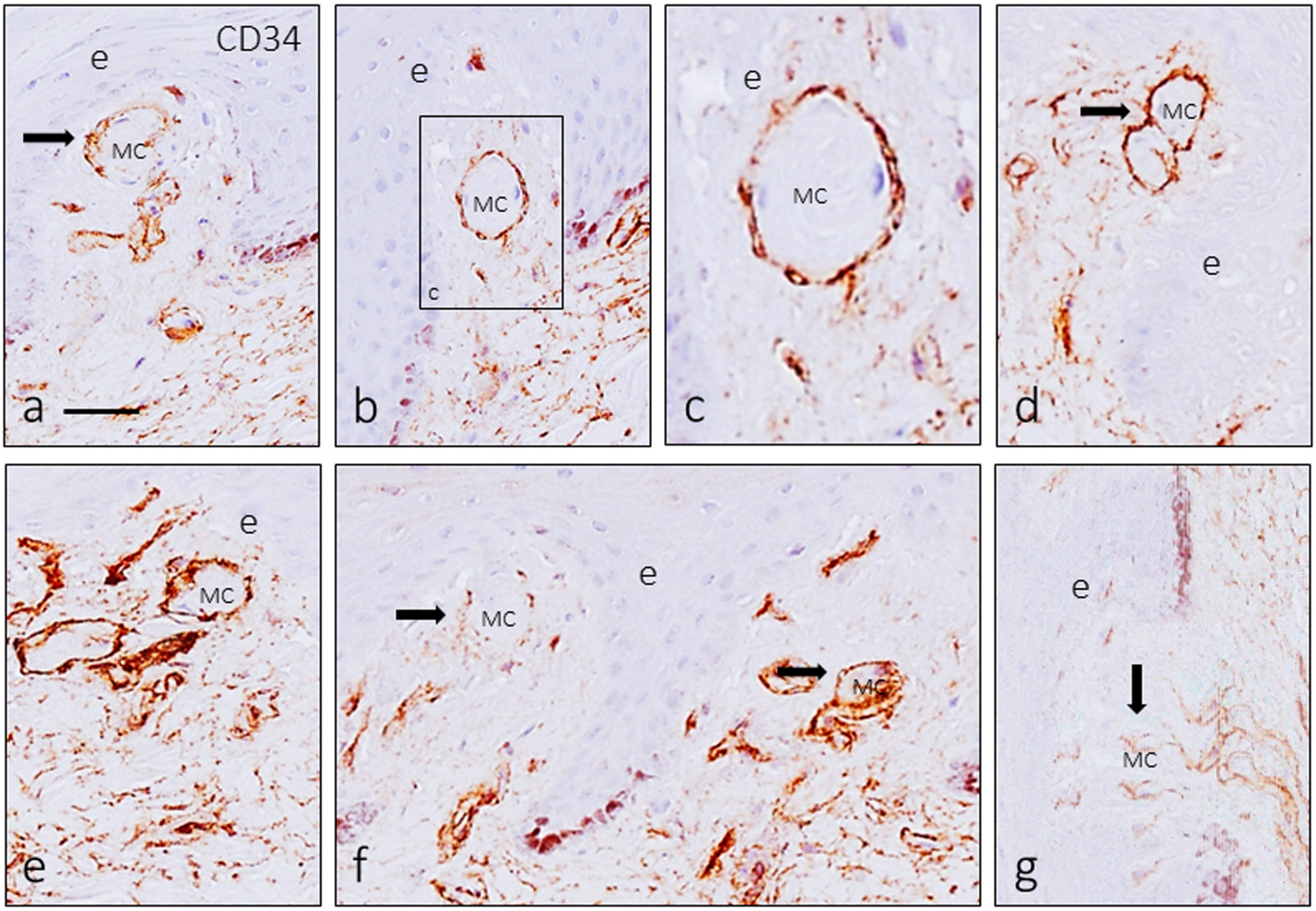

Fig. 4. Miessner corpuscles (MC; indicated by arrows) show a complete or incomplete endoneurial capsule consisting of CD-34 positive cells. e: epidermis; UL: upper lip; LL: lower lip.

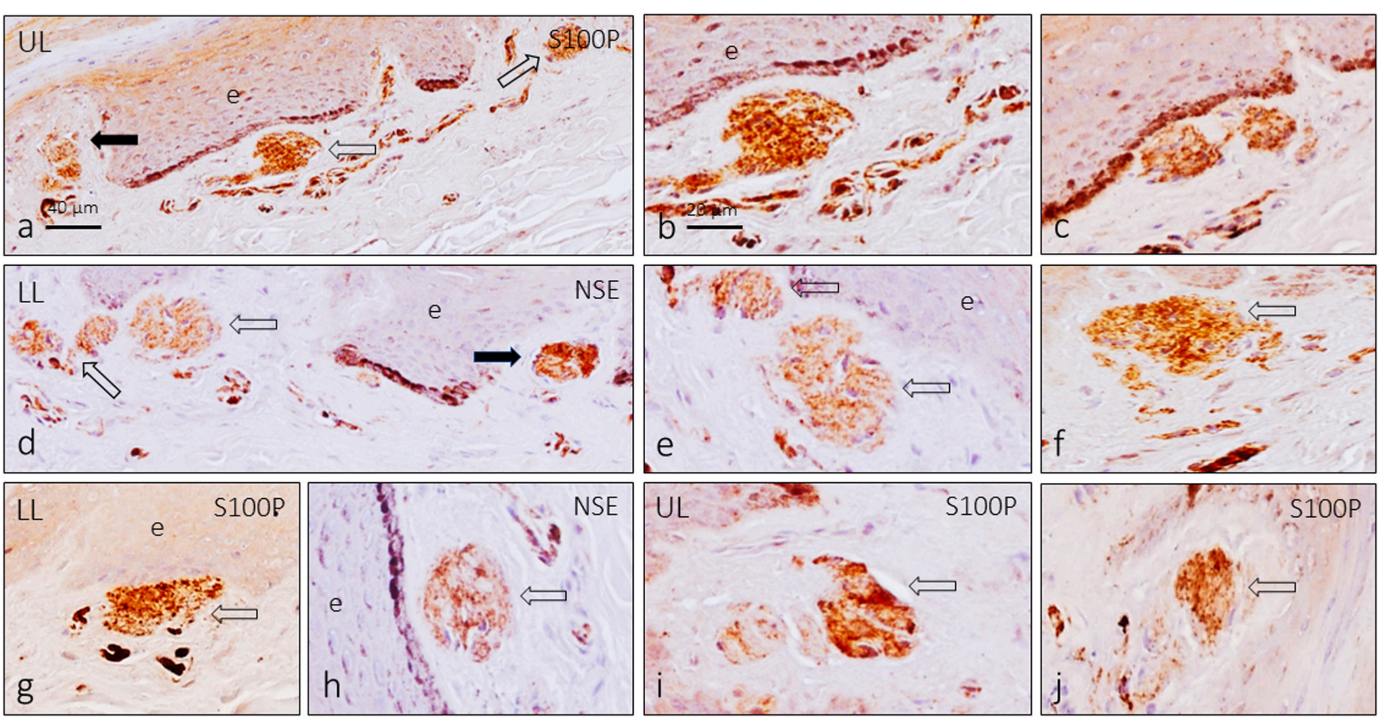

Fig. 5. Different morphotypes of glomerular corpuscles (white arrows) located beneath the epithelium. Black arrows indicate Meissner corpuscles. UL, upper lip; LL: lower lip.

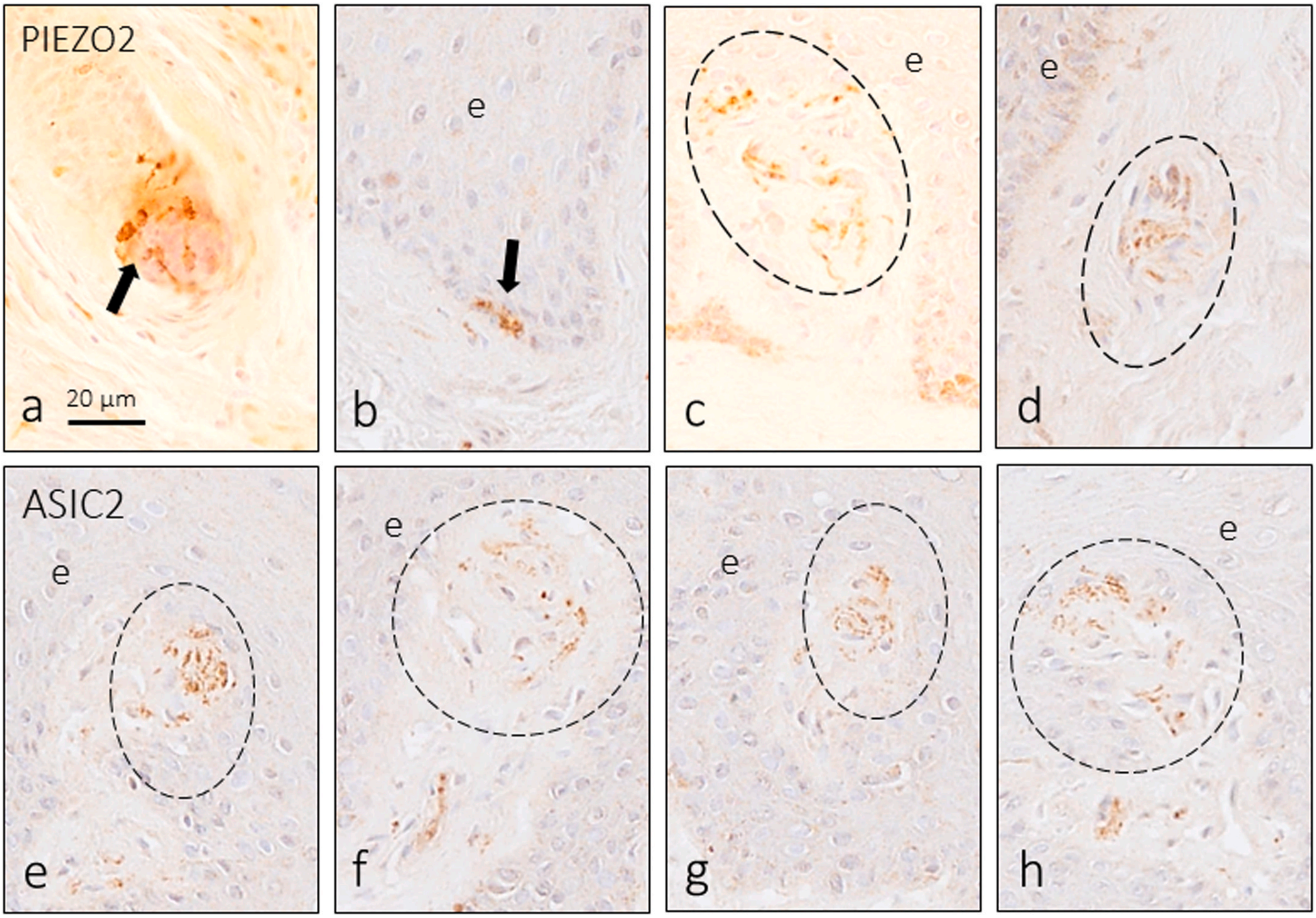

Fig. 6. Immunoreactivity for PIEZO2 is seen in Merkel cells associated with the hair papillae (a) and in the basal layer of the vermilion epithelium (c), as well as the axons of Meissner (b) and glomerular (d) corpuscles. Faint ASIC2 immunostaining was observed in the axons of Meissner corpuscles. e: epidermis.

We also investigated the presence of ion channels related to mechanosensitivity (PIEZO2, ASIC2, and TRPV4) and thermosensitivity (TRPV1, TRPM2, and TRPM8) in the sensory corpuscles of the vermilion. PIEZO2 was detected in cells associated with hair follicles (Fig. 6a), and the isolated cells located in the *stratum basale* of the epithelium (Fig. 6b) were identified as Merkel cells. In addition, fine and faint PIEZO2 immunolabelling was detected in the axons of some Meissner (Fig. 6c) and glomerular (Fig. 6d) corpuscles. Axons displaying immunoreactivity for ASCI2 were also found in the Meissner corpuscles but not in the glomerular corpuscles (Fig. 6e-h). However, immunoreactivity for ion channels TRPV1, TRPV4, TRPM2, or TRPM8 was detected within sensory corpuscles (data not shown).

Non-neural tissues, especially epithelial structures, such as microscopic saliva and sweat glands, exhibited faint immunoreactivity for PIEZO2, TRPV4, and TRPM8 (data not shown).

3.3. Mucosa

Sensory nerve formations with diverse and irregular morphologies, not identifiable as cutaneous or vermilion, were found in the labial submucosa. Occasionally, they resembled glomerular formations, with a dotted pattern of immunoreactivity for axonal and glial markers (Fig. 7a-b). Others exhibited linear (Figs. e-g) or irregular morphologies (Fig. 7c-d), occasionally resembling Meissner corpuscles (Fig. 7h).

4. Discussion

The aim of this study was to comprehensively analyse the innervation of human lips, with particular emphasis on the vermilion. We used various antibodies to identify axons (NSE and NFP), Schwann cells, and terminal glial cells (S100P), as well as the endoneurium (CD34) and perineurium (Glut-1) covering the nerves and sensory corpuscles. Furthermore, we examined the potential functional implications of sensory corpuscles by investigating the presence of ion channels associated with mechanosensation (ASIC2, PIEZO2, and TRPV4) and thermosensation (TRPV1, TRPM2, and TRPM8) (Cobo et al., 2021; Martín-Alguacil et al., 2021).

While recent studies on the microscopic innervation of human lips have primarily focused on punch biopsies, particularly the detailed work by Nolano et al. (2013), the current study focused on the vermilion, labial hairy skin, and mucosa. Our results partially align with those of Nolano et al. (2013), including the identification of Ruffini-type corpuscles associated with the papillae of hair follicles, Meissner corpuscles in the vermilion, and enigmatic sensory corpuscles in the labial mucosa. However, complex Merkel neurite cells were not observed in our study. Notably, Nolano et al. (2013) did not report the occurrence of glomerular corpuscles, which were the most abundant in our study. These discrepancies can be attributed to our comprehensive analysis of whole lips, a distinction from the small biopsy samples analysed by Nolano et al. (2013) that excluded the vermilion.

The vermilion is widely acknowledged as the most densely innervated part of the lip (Rath and Essick, 1990), forming the primary focus

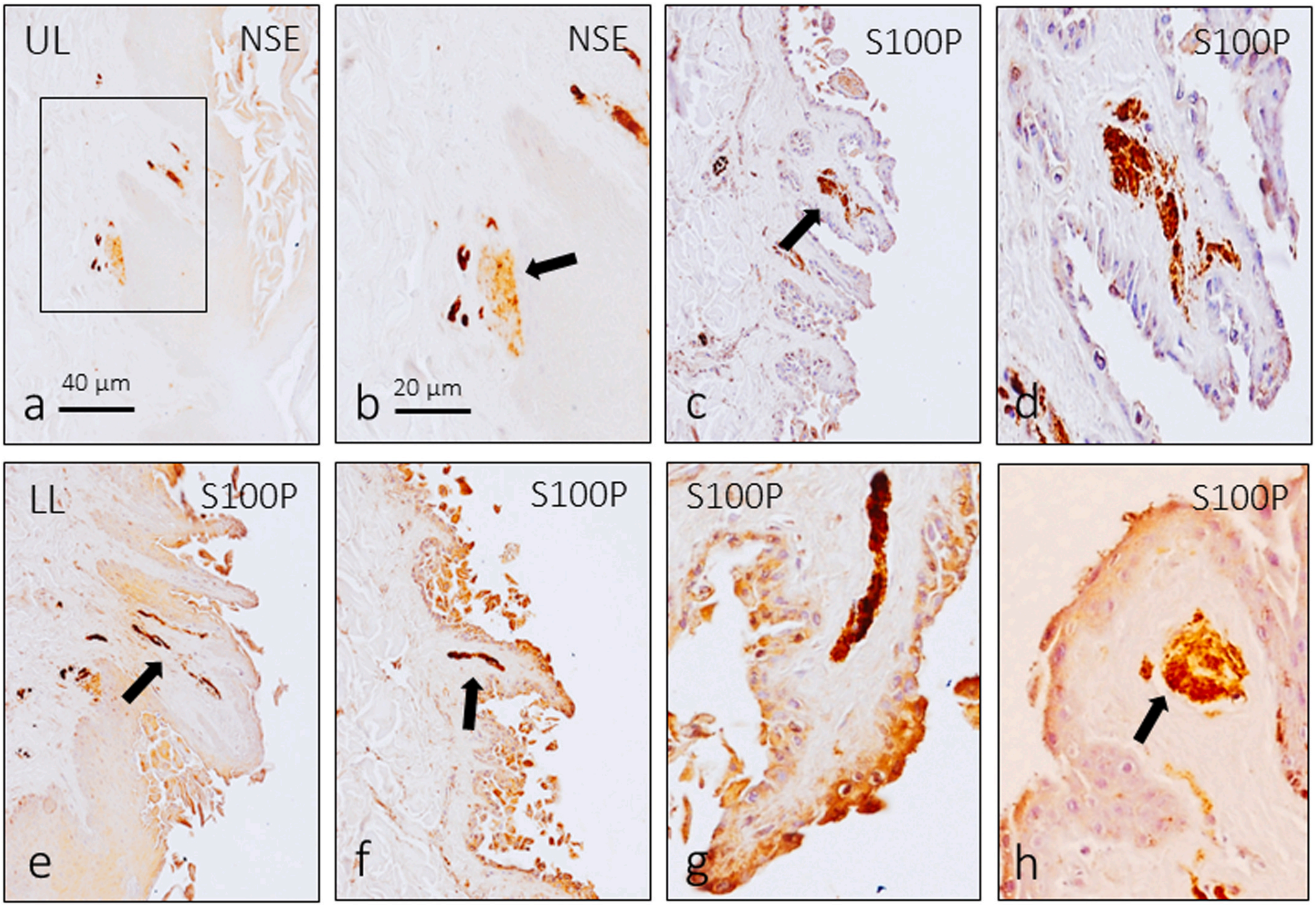

Fig. 7. Different morphotypes of sensory corpuscles in the lip mucosa. The sensory corpuscles in the labial mucosa exhibited irregular morphologies (c, d, and h), sometimes resembling glomerular corpuscles (a and b). UL: upper lip; LL: lower lip.

of our study. Somatosensory afferents can be classified morphologically based on their sensory terminals or sensory corpuscles, and functionally classified based on the conduction speed of their action potentials (Rice and Albrecht, 2008; Zimmerman et al., 2014; Cobo et al., 2021; Martín-Alguacil et al., 2021). We observed Meissner and cutaneous Ruffini-like corpuscles, which can be associated with type I RALTMRs and type II SA LTMRs potentials, respectively, recorded in the lips in microneurography studies. However, we did not detect Merkel cell-neurite complexes that are associated with type I SA LTMRs (Trulsson and Johansson, 2002; Bukowska et al., 2010; Trulsson and Essick, 2010). Although glomerular corpuscles (also known as glomerular bodies, capsulated glomerular terminations, or genital nerve body type I; Seto, 1963) are most abundant in the vermilion, their functional role remains unclear. A recent study by Qi et al. (2023) created equivalents of the glomerular and Krause corpuscles of mucocutaneous tissues, such as the glans penis, clitoris, and tongue. They demonstrated that Krause corpuscles in the murine penis and clitoris are RA LTMRs. Nevertheless, future studies are necessary to verify whether human vermilion glomerular corpuscles also serve of the human lips also serve as mechanoreceptors, and to establish the functions of labial mucosa sensory corpuscles.

The mechanotransduction process in sensory corpuscles involves mechano-gated ion channels (Wu et al., 2017; Douguet and Honoré, 2019; Jin et al., 2020; Kefauver et al., 2020), which are present in the axons of human cutaneous sensory corpuscles (Cabo et al., 2015; García-Mesa et al., 2021a, 2021b, 2022a, 2022b; Cobo et al., 2020). In the present study, we extended this understanding by reporting the presence of PIEZO2 and ASIC2 in the axons supplying the Meissner and glomerular corpuscles in the vermilion, thus supporting their association with mechanoreceptors. However, we could not confirm thermosensitivity in vermilion sensory corpuscles because TRPM2 and TRPM8 were not detected in them. As previously speculated, the Krause corpuscles (glomerular corpuscles) are not thermosensors in mice. Further research is required to identify the structures responsible for the high thermal sensitivity of human vermilions.

Somatosensory afferents in the lips respond to contact with environmental objects, contact between the lips, changes in air pressure generated for speech sounds, and deformations that accompany the lips during chewing and swallowing. Additionally, it has been proposed that labial afferents also provide proprioceptive information (Trulsson and Johansson, 2002; Ito and Gomi, 2007).

Collectively, the present study provides evidence that the sensory corpuscles in the vermilion of human lips represent the sensory organs of mechanoreceptors which engage in all functions of the lips.

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Ethical statement

This study was approved by the Ethics Committee for Biomedical Research of the Principality of Asturias, Spain (Cod. CElm, PAst: Proyecto 266/18).

CRediT authorship contribution statement

JM-P, YG-M, and PC performed the experiments. BM-B and OG-S collected the material in compliance with ethical guidelines and contributed to the experimental work. JLC and OG-S conducted the quantitative analyses. JM-C and JAV designed the study, analysed the data, and wrote the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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