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The disturbed expression of vitamin D and retinoic acid-related orphan receptors α and γ and of megalin in inflammatory skin diseases

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Abstract

The pathogenesis of inflammatory skin diseases is associated with the abnormal activity of keratinocytes and immune cells infiltrate. Vitamin D_3 deficiency can correlate with the increased incidence, severity, and duration of inflammatory skin disorders. The exact mechanism on how vitamin D_3 influences inflammatory skin diseases still requires clarification. However, it can be associated with the disturbances in transmembrane glycoprotein - LRP2/megalin, which is implicated in vitamin D_3 transport to the cell, and defects in vitamin D-signaling through the nuclear receptors. Therefore, by using immunohistochemistry, we analyzed the expression of LRP2/megalin, VDR, RORα and RORγ in allergic contact dermatitis, lichen simplex chronicus, sarcoidosis and psoriasis in comparison to the normal skin. We observed decreased expression of LRP2/megalin in all inflammatory lesions in comparison to the normal skin. Significant differences were also noticed in VDR, RORα and RORγ levels between inflammatory lesions and normal skin. Our research indicates disturbed expression of LRP2/megalin, VDR, RORα and RORγ in inflammatory skin lesions in comparison to normal skin. Therefore, we suggest that changes in the activity of these proteins may play role in pathogenesis of inflammatory skin disorders. Furthermore, we suggest that LRP2/megalin, VDR, RORα and RORy may serve as targets in therapy of these diseases.

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Authors' contributions

AAB - designed the study, performed experiments, evaluated immunohistochemically stained samples, interpreted the data, and wrote the paper; MŻ, KL, RMS - took part in data collection/analysis and preparation of the manuscript; A.T.S. designed the study, provided the material for the experiments, coordinated the experiments, analyzed data, worked on the manuscript, and secured the funding. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Keywords

vitamin D; nuclear receptors; megalin; sarcoidosis; lichen simplex chronicus; psoriasis; allergic contact dermatitis

Background

The skin serves as a barrier between the environment and the inner part of the organism, and plays a crucial role in the defense against pathogens, chemicals, and/or physical stressors, as well as maintaining the body's homeostasis[1]. The skin is also a significant part of immune system[2]. It is engaged in the development of anti-microbial resistance, autoimmunity and inflammatory skin conditions, allergies or tumor immunity[3]. The cutaneous immune surveillance includes innate and adaptive immune responses[4].

There is increased evidence that the impaired regulation of immune skin functions underlies the pathogenesis of wide range of cutaneous disorders. For example, psoriasis is one of the most commonly diagnosed inflammatory skin diseases[5] with worldwide prevalence of about 2%[6]. This disorder manifests as inflammatory lesions with epidermal hyperplasia and immune cells infiltration[7]. One commonly used treatment for psoriasis, ultraviolet B phototherapy, inhibits the inflammatory responses, while stimulating vitamin D formation in the skin[8]. Vitamin D_3 is activated by two-step hydroxylation catalyzed by cytochrome P450 enzymes including CYP2R1 and CYP27A1 with final C-1α hydroxylation by CYP27B1, to produce $1,25(OH)_2D_3$, or by sequential hydroxylation of the side chain by CYP11A1[9, 10]. These pathways are also expressed in the skin[11, 12] and immune system[13].

About 40% of the European population suffer from vitamin D_3 deficiency[14], which can be linked to autoimmune disorders[15]. Vitamin D_3 has immunomodulatory effects by regulation of T cells[16–18] and is implicated in the regulation of both the innate and adaptive immunity[16]. Several studies have shown a relationship between decreased levels of vitamin D_3 and incidence of autoimmune skin disorders[19–21], severity of psoriasis[22–24] and atopic dermatitis[25]. In addition, polymorphism in vitamin D receptor (VDR) gene has been implicated in both severity [26] and susceptibility[27,28] to psoriasis.

Vitamin D_3 is transported by the group-specific component vitamin D binding protein (GC/DBP)[29]. GC/DBP is a ligand for LRP2/megalin (low density lipoprotein-related protein 2), which is a transmembrane glycoprotein[30]. LRP2/megalin is involved in reabsorption and further metabolism of chemicals and small proteins, including vitamins transfer proteins[31]. Previous research has indicated an unambiguous relationship between LRP2/megalin and vitamin D_3 endocytosis[32] and activation of genomic and non-genomic responses[33]. LRP2/megalin is implicated in regulation of 25(OH)D uptake by kidneys[32]. It is therefore likely that there is connection between LRP2/megalin expression and vitamin D in psoriasis development.

Questions addressed

To exert the phenotypic activities, active forms of vitamin D_3 must interact with VDR[11, 34]. More recently, it was reported that retinoic acid-related orphan receptors α and γ (RORα

and RORγ, coded by *RORA* and *RORC* genes, respectively) are targets for regulation by vitamin D_3 hydroxyderivatives[34], acting as inverse agonists on RORα and RORγ. RORα and RORγ are expressed both in normal and pathological skin[34, 35]. RORs are implicated in wide variety of cell functions[36], and can play a role in inflammatory skin disorders[37]. Therefore, to gain an insight into vitamin D endocrine system in inflammatory skin diseases, we analyzed the expression of LRP2/megalin, VDR, RORα and RORγ in psoriasis, allergic contact dermatitis (ACD), lichen simplex chronicus (LSC) and sarcoidosis.

Experimental design

For immunohistochemistry skin samples of ACD, LSC, sarcoidosis, psoriasis and normal skin was included into this study (Table 1). The authors declare that this investigation was carried out following the rules of the Declaration of Helsinki of 1975 (revised in 2008) and this study was approved by the Institutional Review Board of the UAB under IRB-940831016 (OCCC Tissue Procurement CORE Facility) and IRB-00000726 (Title E150427002, Dr. A. Slominski PI). The IRB of the UAB, which gave their permission for conducting this study, waived the requirement to obtain Patients' informed consent for this research.

The samples were stained for LRP2/megalin, VDR, RORα and RORγ antigens as previously described[34, 35, 38, 39]. Detailed data are presented in the Supplementary file and Supplementary Table 1. The immunostained sections were assessed using semiquantitative scoring systems using both the percentage of immunoreactive cells (IR) and the staining intensity (SI) from 0 to 3 arbitrary units (A.U.) according to the following formula SQ=mean(IR x SI)/100. Statistical comparison of subgrouped data were performed with GraphPad Prism software (version 5.0; GraphPad Software, La Jolla, CA, USA).

Testing of the expression of VDR, RORα and RORγ in HaCaT keratinocytes was performed using western blot according to the procedure presented in Supplementary file.

The analysis of the expression of VDR, RORα, RORγ and LRP2/megalin on mRNA level followed public genomics data repository (https://www.ebi.ac.uk/gxa/home) and project characterized in [40] (for details see Supplementary file). The comparisons between the psoriatic individuals and healthy controls were performed using t-test with $P<0.05$ considered to indicate a statistically significant difference.

Results

The expression of all tested markers was detected using immunohistochemistry in skin compartments. VDR showed predominant nuclear immunostaining, RORα and RORγ showed strong nuclear and weak cytoplasmic immunostaining, and LRP2/megalin showed cytoplasmic location. The representative images of immunostained sections are in Fig. 1. The strong nuclear stain vs weak cytoplasmic was further validated by western blot using antibodies against VDR, RORα and RORγ (Supplementary Figure 1).

In ACD, the reduced levels of VDR, RORα and RORγ and LRP2/megalin in lesional skin were observed in comparison to normal skin (Fig. 2). The expression levels of analyzed receptors in lymphocytes was higher than in lesional keratinocytes (Fig. 2A).

In LSC the lower levels of VDR, RORα, RORγ and LRP2/megalin were found in comparison to normal skin (Fig. 2A). In lymphocytes VDR levels were low and comparable to that observed in lesional epidermis, while RORγ expression was as high as in normal epidermis (Fig. 1).

In sarcoidosis, the expression of RORα and RORγ in lesional skin and lymphocytes was as high as in normal tissue, while in granulomas RORα and RORγ levels were reduced when compared to lymphocytes. VDR and LRP2/megalin levels were significantly reduced in pathological cells and granulomas (Fig. 1). VDR levels in lymphocytes were also reduced in comparison to normal skin.

Levels of VDR and RORα were similar in psoriatic and normal (control) skin (Fig. 2A). RORγ levels in psoriatic keratinocytes were comparable to normal epidermis, being elevated in lymphocytes (Fig. 1 2A). However, LRP2/megalin was significantly reduced in lesional in comparison to the normal skin (Fig. 2A). Analysis of the data from Expression Atlas (https://www.ebi.ac.uk/gxa/home) has shown similar expression of *VDR* mRNA in psoriasis in comparison to normal skin, with expression of *RORA* and *RORC* and *LRP2/megalin* mRNA being lower in lesional than in normal skin (Fig. 2B). The gene expression pattern for the *VDR* and *LRP2/megalin* was consistent with the corresponding protein expression levels.

Conclusions & perspectives

In the present study, we investigated the expression of VDR, RORα and RORγ and LRP2/megalin in inflammatory skin diseases to determine the expression pattern for these receptors and their potential to serve as a predictive targets or markers for vitamin D-based therapies. On the protein level, we observed the reduced expression of LRP2/megalin in all analyzed skin lesions, the reduced RORα and RORγ level in ACD and LCS, the reduced VDR level in lichen simplex chronicus, ACD and sarcoidosis. The immunostaining pattern in all analyzed lesions and normal skin for VDR, RORα and RORγ and LRP2/megalin was similar. Up to now, there is shortage of information on the expression of analyzed proteins in the skin samples of inflammatory cutaneous diseases. To the best of our knowledge, our data is the first time that describes the expression of RORα and LRP2/megalin in inflammatory skin diseases and RORγ in skin samples of these diseases.

Some studies reported that psoriasis patients have reduced vitamin D3 levels[24, 41]. Vitamin D can regulate the proliferation and growth of keratinocytes[17, 42–44], and it was also successfully incorporated as an adjuvant treatment for psoriasis[26, 45]. The therapeutic action of the active forms of vitamin D is mediated by its receptor, VDR. Additionally, the *VDR* polymorphism is linked to psoriasis susceptibility [27,28] and susceptibility of psoriatic patients to the vitamin D-based treatment. The reduced VDR levels in psoriatic skin are related to the reduced tight junctions[46]. It has been suggested that such disturbances can

affect the maintenance of skin homeostasis[46]. *VDR* polymorphisms can also be considered as genetic risk factors for sarcoidosis[47] with no effects of *VDR* SNPs on severity of sarcoidosis[48], oral lichen planus[49] and atopic dermatitis[50]. The expression of VDR in inflammatory skin diseases is altered, but some study showed contradictory data. Kim et al[51] observed the gradual decrease of VDR expression from normal skin to atopic dermatitis, from perilesional skin to psoriatic lesion. However, recent study showed that VDR is present in psoriatic skin with its predominantly strong expression[52]. The differences between these studies could result from the different antibodies used for the VDR detection. This consideration is supported by similar results of our study with the study by Milde et al[53], who used 9A7 clone of VDR antibody and showed comparable level of VDR in normal and psoriatic skin.

The expression of RORγ in inflammatory skin diseases is usually reported in peripheral blood samples since RORγt is a crucial receptor for the differentiation of Th17 cells[54], that play essential role in the pathogenesis of psoriasis and other chronic inflammatory processes of the skin[55]. Ecoeur et al[56] showed that selective RORγt inhibitor, Cpd A, inhibited Th17 pathway and the production of pro-inflammatory cytokines by T-cells and reduced IL-17-induced responses in keratinocytes. It has been proposed that RORγt can be molecular target for the psoriasis treatment[57]. In mouse models of atopic dermatitis and acute irritant dermatitis, synthetic RORα/γ inverse agonist - SR1001, exerted anti-inflammatory effects, restored epidermal barrier affecting multiple cell types in the skin[58]. Our previous study showed that RORγ and RORα are expressed in human skin and can serve as receptors for vitamin D derivatives[34]. In this study we found that RORα and RORγ are present in inflammatory skin diseases, however their expression was disturbed, suggesting that impaired RORα and RORγ expression can be involved in pathogenesis of inflammation.

LRP2/megalin may be crucial for proper cell development and differentiation[59]. Its expression was detected in normal skin, hair follicles[60] and melanoma cells[61]. Our data showed the reduced LRP2/megalin levels in lesional cells in comparison to normal skin. Therefore, we suggest that the reduced expression of LRP2/megalin can be involved in pathogenesis of psoriasis and other inflammatory skin disorders through reduction of endocytosis and intracellular vitamin D3 signaling in affected skin cells.

In summary, the expression of VDR, RORα and RORγ and LRP2/megalin is aberrant in inflammatory skin diseases. We suggest that the disturbances in their expression are related to the pathogenesis of ACD, LSC, sarcoidosis and psoriasis. In addition, the presence of these receptors in the skin should allow to target them for vitamin-D based therapies of the inflammatory skin diseases providing a background for future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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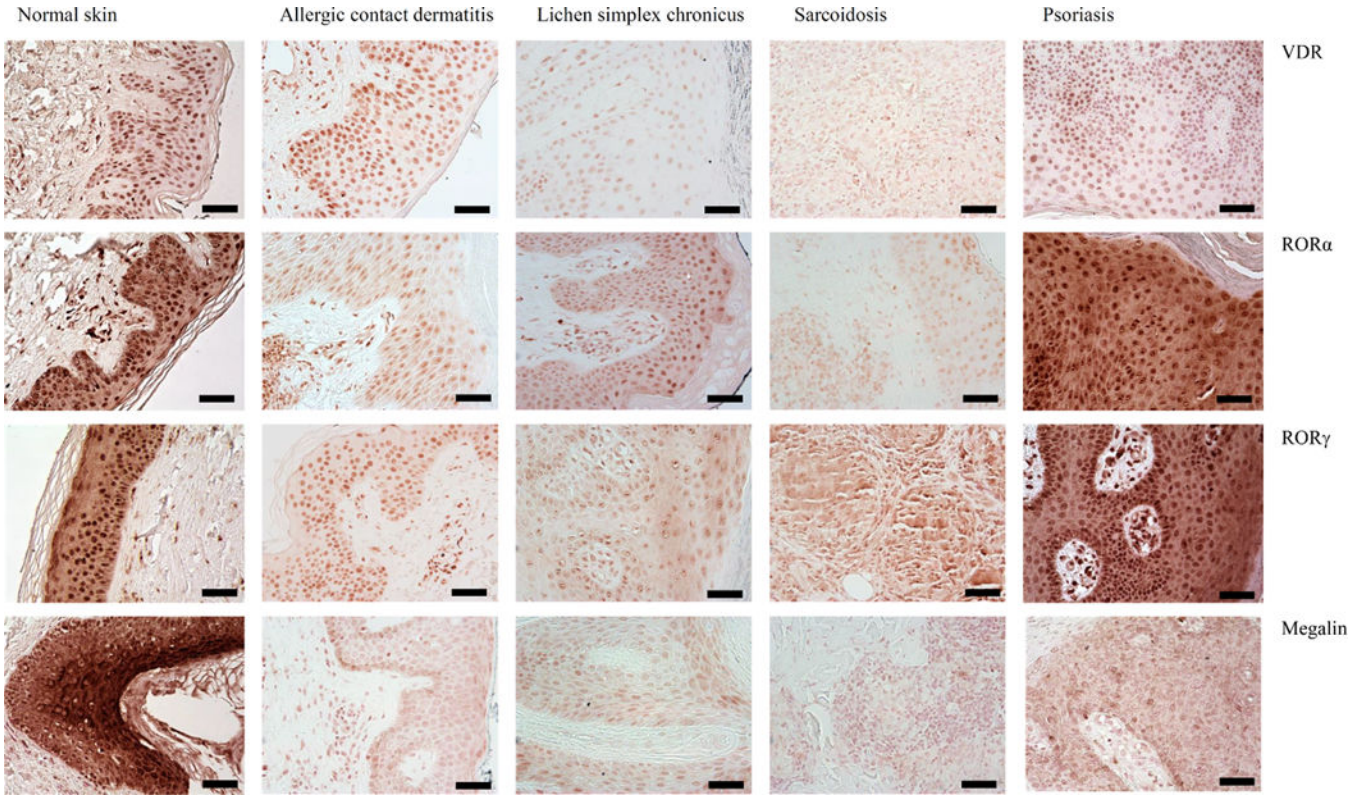

Figure 1.

Representative images of immunostaining of VDR, RORα and RORγ and LRP2/megalin in allergic contact dermatitis, lichen simplex chronicus, sarcoidosis and psoriasis. Scale bars: = 50 μm.

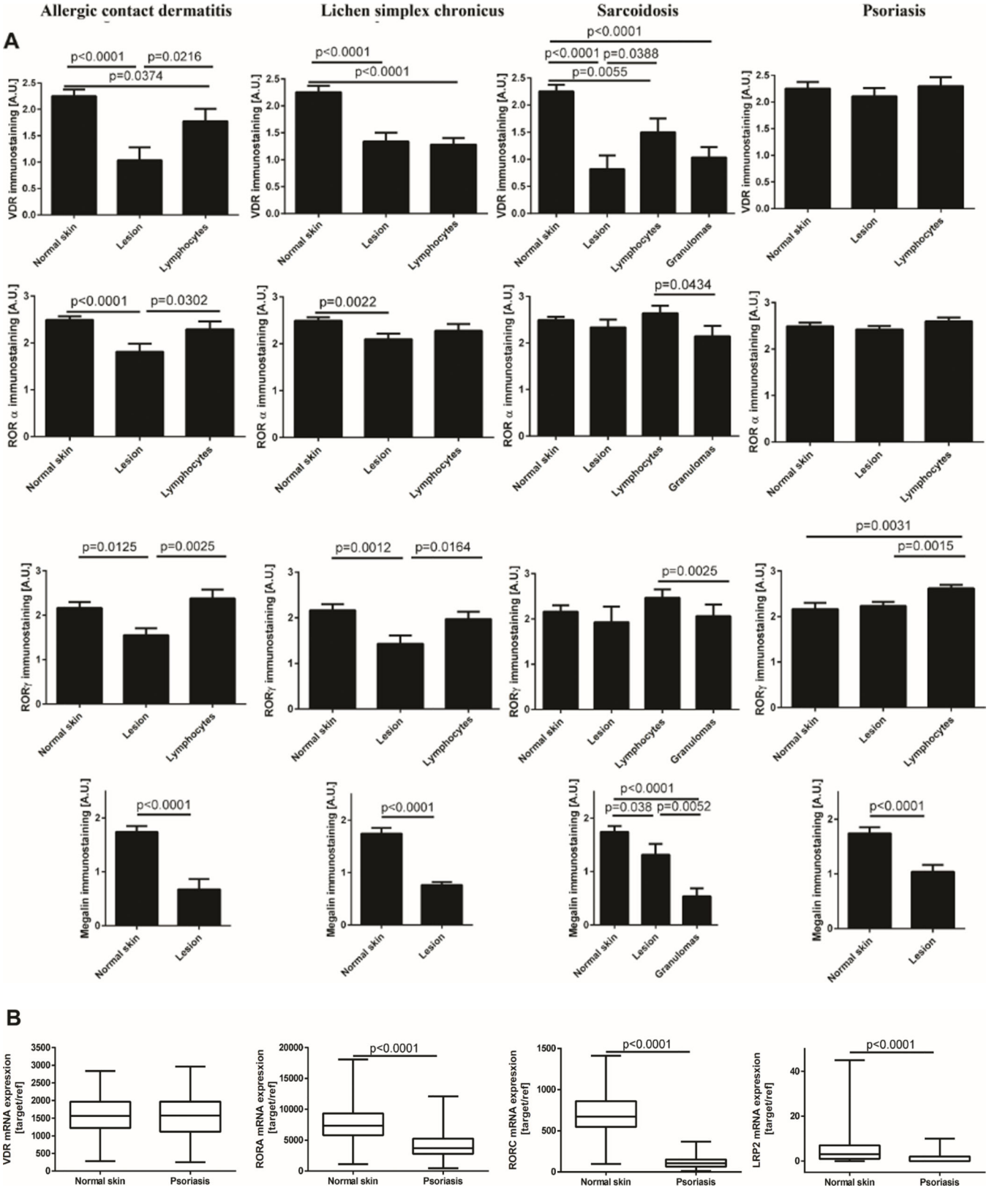

Figure 2.

Expression levels of VDR, RORα and RORγ and LRP2/megalin. A) The expression measured by immunohistochemistry in psoriasis, allergic contact dermatitis, lichen simplex chronicus and sarcoidosis. Statistically significant differences are denoted with p values as determined by Student's *t*-test. B). The expression measured by RNA-seq in psoriasis and normal skin (https://www.ebi.ac.uk/gxa/home; [40]).

Table 1.

Characteristic of normal skin (control) and lesional skin samples.

	Normal skin (control)	Psoriasis	Atopic contact dermatitis	Lichen simplex chronicus	Sarcoidosis
Number of cases	36	26	10	18	8
Sex (F/M)	17/9 *	12/14	2/8	3/13 **	5/1****
Age (mean [range])	44.3 (20–68) *	52.7 (20–86)	50.6 (20–62)	51.1 (34–70)	#
Location	*			**	***
Head (forehead, jaw, chin, temple, scalp)	2	1		6	
Neck	1			4	
Leg	2	4	3	1	1
Arm		7			4
Hand	1		1		
Breast	6			2	
Back	1	6	1	1	1
Abdomen	11	6			
Foreskin	2				
Other		2	5	2	
Immunostaining					
VDR	34	26	10	17	7
LRP2/megalin	26	26	10	18	8
RORα	33	26	10	18	7
RORγ	31	26	10	18	7

* data available for 26 cases

** data available for 16 cases

*** data available for 6 cases

lack of the data

Number of samples stained for VDR, megalin and RORs differs due to lack of representative of lesional areas in the sections.