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Atopic Dermatitis Related to *RNF31* Genetic Variant

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Abstract

Atopic dermatitis is a chronic and inflammatory skin disease and the most severe forms could strongly impact the patient's quality of life. Skin barrier dysfunction is considered the first step in the atopic march. *RNF31* deficiency significantly changes the skin structure and increases its thickness. The keratinocytes show decreased expression of K10 and loricrin. In this way, *RNF31* deficiency alters the proper functioning of the skin by altering the homeostasis of keratinocytes. We present the case of a 2-year-old boy diagnosed with severe atopic dermatitis, with impaired quality of life due to a genetic variant related to keratinocyte function that has not been previously reported in humans with atopic dermatitis.

Subject Areas

Allergy, Clinical Immunology, Dermatology, Pediatrics

Keywords

Atopic Dermatitis, Genetics Variant, Skin Disease, Keratinocytes

1. Introduction

Atopic dermatitis is a chronic and inflammatory skin disease and the most severe forms could strongly impact the patient's quality of life [1]. Skin barrier dysfunction is considered the first step in the atopic march. One of the most studied proteins is filaggrin, the major protein of the stratum corneum, encoded by the FLG gene. When there is a dysfunction, it has been associated with an increased risk of severe atopic dermatitis, onset in early life, and persistence of

symptoms, in addition to skin infections. This skin barrier dysfunction, accompanied by type 2 inflammation and the production of IL-4 and IL-13 cytokines, plays an important role in the inflammation that occurs in the disease [2]. As an immunological barrier, the stratum corneum provides an effective defense; in this stratum, keratinocytes move towards the surface to become corneocytes and secrete the contents of the lamellar bodies to form the layer [3]. Therefore, the integrity of corneocytes and keratinocytes is important for the proper functioning of the skin and its immune barrier function.

The treatment of atopic dermatitis varies depending on the degree of severity. In cases of mild dermatitis, measures focused on skin care should be followed, including the use of necessary emollients. In severe cases, immunomodulatory drugs or monoclonal antibodies such as dupilumab, tralokinumab, baricitinib or upadacitinib can be used with the aim of inhibiting interleukins or inflammatory mediator proteins [4].

We present the case of a 2-year-old boy diagnosed with severe atopic dermatitis, with impaired quality of life due to a genetic variant related to keratinocyte function that has not been previously reported in humans with atopic dermatitis. The purpose of this case report is to identify new pathways and genetic variants in atopic dermatitis immunopathology.

2. Clinical Case

A 2-year-old boy, the son of Latino parents, began with eczema spreading to the entire skin from birth, with greater intensity on the buttocks and face. The lesions had been treated with topical steroids and came to require hospitalization with the need for systemic steroid application. At one month of age, he began with an increase in eczema related to the intake of breast milk, so the mother started a dairy-restricted diet without milk and derivatives with adequate improvement. Six months later, a complementary diet with cow's milk was started, which once again produced an increase in eczema lesions. The mother recognizes that various foods can exacerbate the symptoms, however, she does not identify them. He went to the allergy clinic where the diagnosis of severe atopic dermatitis was issued without performing another approach. When he was re-evaluated in our medical center, we found it relevant that the patient had been born with dentition in addition to the discovery of a supernumerary bone in the right carpus (**Figure 1**).

We requested the ALEX macro assay study to determine molecular sensitization to allergens and began treatment with cutaneous calcineurin inhibitors (pimecrolimus 1%) and strict skin care measures. Taking the results of the ALEX study, we found positivity to various food proteins and serum immunoglobulin E levels at 2534 kU/L (normal for ages up to 16 kU/L), the results are shown in **Table 1**.

With this result and the suspicion of a probable inborn error of immunity related to a Hyper IgE syndrome, we requested new generation gene sequencing

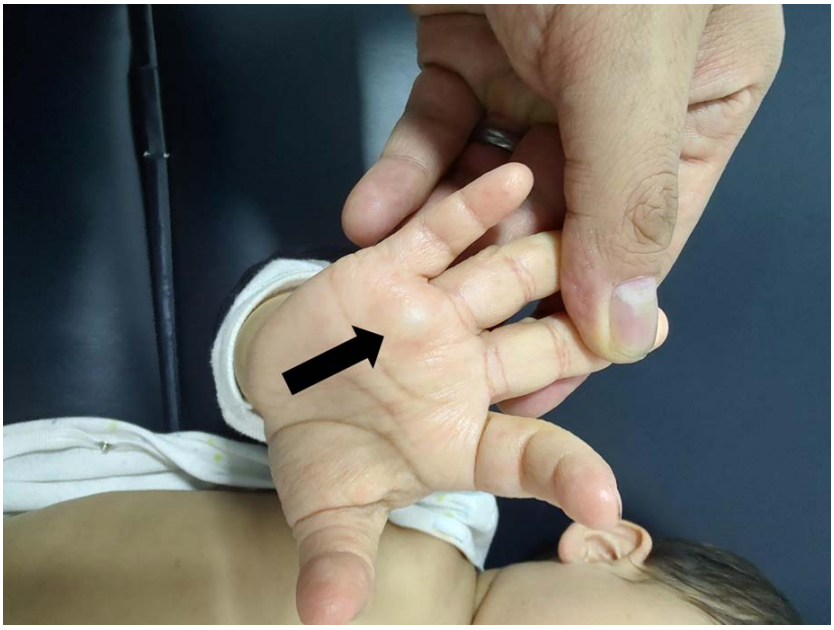

Figure 1. The arrow shows the supernumerary bone identified by palpating the patient's hand.

Table 1. Results of the molecular allergy study showing the positive IgE levels for each food protein (Negative < 0.3 kUA/L).

Allergen	Nomenclature	Protein group	Results (kUA/L)
Peanut	Ara h 1	7/8S Globulin	0.64
	Ara h 3	11S Globulin	2.61
Soy	Gly m5	7/8S Globulin	0.76
	Gly m6	11S Globulin	0.81
Oatmeal	Ave s		1.47
Rice	Ory s		1.2
Wheat	Tri a 14	nsLTP	27.05
	Tri 1 19	Omega-5 gliadin	4.51
Cow milk	Bos d 4	*α*-lactalbumin	10.44
	Bos d 5	*β*-lactoglobulin	0.3
	Bos d 8	Casein	50
Egg	Gal d 1	Ovomucoid	29.9
	Gal d 2	Ovalbumin	47.77
	Gal d 3	Ovotransferrin	10.22
	Gal d 4	C lysozyme	35.23
Atlantic mackerel	Sco s 1	*β*-palvalbumin	10.25

(Invitae Inborn Errors of Immunity and Cytopenias Panel) with a report of two gene variants, one in the *ADAR* gene c.1177A > G (p.Asn393Asp), related to Aicardi-Goutières syndrome and *RNF31* (Ring finger protein 31) c.3097T > C (p.Tyr1033His), we ruled out genetic variants related to Hyper IgE syndrome; both variants were classified as of uncertain significance. In the analysis and spe-

cialized review of the case, the patient does not meet the criteria to classify the disease as Aicardi-Goutières syndrome, however, the alteration in *RNF31* is striking.

With treatment, the patient has an improvement in skin symptoms, as can be seen in Figure 2. However, he must continue to be monitored for the genetic variant found.

3. Discussion

To date, there is no proven relationship in humans between genetic variants in *RNF31* and atopic dermatitis.

Ubiquitination is a reversible process that involves the addition of ubiquitin to a substrate by an enzymatic process. Polyubiquitinated chains are created when an N-terminal (M1) lysine or methionine residue on a ubiquitin residue itself is ubiquitinated; the formation of the M1-linked ubiquitin chain is catalyzed by the linear ubiquitin chain assembly complex (LUBAC) [5]. This complex consists of an *RNF31* catalytic subunit named HOIP (HOIL-1L interacting protein) and two associated molecules, HOIL-1 and SHARPIN (SHANK Associated RH Domain Interactor). Some studies have shown that *RNF31*-deficient mice are not viable in the embryonic period [6]. When the immunohistological analysis of *RNF31* knockout mice is initially performed with the wildtype, no structural differences are found in the skin, but when the mice grow up, *RNF31* deficiency significantly changes the skin structure and increases its thickness, the keratinocytes show decreased expression of K10 and loricrin. In this way, *RNF31* deficiency alters the proper functioning of the skin by altering the homeostasis of keratinocytes [7].

HOIP deficiency has been previously reported, Boisson *et al.* reported the case of a 19-year-old woman with autoinflammation of multiple organs, systemic lymphangiectasia, limb weakness, and combined manifestations of immunodeficiency with amylopectinosis [8]. Oda *et al.* reported a case of an 8-year-old patient with common variable immunodeficiency (CVID) and systemic inflammation without evidence of lymphangiectasia or amylopectinosis unlike the first case [9].

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ADAR	c.1177A>G (p.Asn393Asp)	heterozygous	Uncertain Significance
RNF31	c.3097T>C (p.Tyr1033His)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 574 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 2. Results of gene variant (Invitae Inborn Errors of Immunity and Cytopenias Panel).

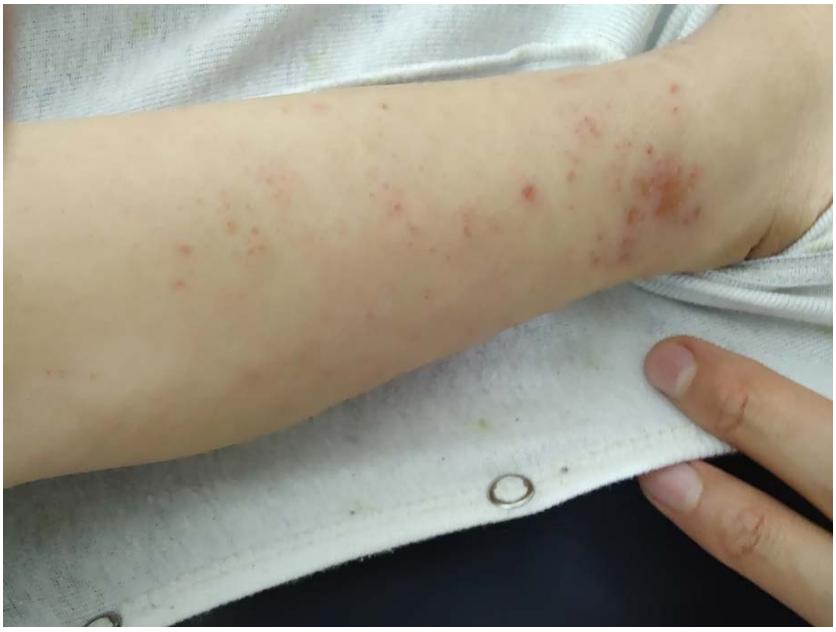

Figure 3. Skin in recovery, after the indicated treatment. Small areas of eczema are observed.

The clinical case that we report is relevant since the database of the laboratory where the study was carried out considers the single nucleotide variant as of uncertain significance (**Figure 2**), however, the presentation of this patient's case is associated with food allergy. and skin manifestations that coincide with the described pathophysiology of atopic dermatitis and alteration in the integrity of the skin layers. The patient is in partial control of atopic dermatitis (**Figure 3**) but must maintain vigilance for the appearance of new symptoms and complications in the future.

The expression of *RNF31* has been demonstrated in the colon and theoretically, if there is an alteration in the structure and function, it can also affect cell integrity and thus contribute to the appearance of food allergy, and alterations in the intestinal barrier, as happened in our patient [10]. *RNF31* has previously been shown to interact with *FOXP3* and to be positively associated with regulatory T-cell function [11].

4. Conclusions

Genetic variants in the *RNF31* gene are related to defects in keratinocytes and intestinal epithelium.

The alterations in the protein complexes may suggest that these alterations are the cause of the epidermal dysfunction in atopic dermatitis.

The alteration in intestinal epithelial permeability and, the increase in the excessive production of IgE may be related to the predisposition to generate food allergy at an early age.

It is necessary to determine the proteins of the LUBAC complex to understand if the function is compromised in patients with genetic variants in *RNF31*.

Conflicts of Interest

The authors declare no conflicts of interest.

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