Dermal IgA Is Rare in Celiac Disease and Relatives and Lacks Dermatitis Herpetiformis-Type Colocalization with Transglutaminase 3

JID Open

Journal of Investigative Dermatology (2025) ■, ■–■; doi:10.1016/j.jid.2025.09.380

TO THE EDITOR

Dermatitis herpetiformis (DH) is a blistering and itching skin disease and an extraintestinal manifestation of celiac disease (CeD), a gluten-driven autoimmune enteropathy (Reunala et al, 2021). The risk for DH and CeD runs in families owing to shared genetic predisposition. Hallmark for DH is dermal granular IgA deposition detected with direct immunofluorescence (DIF) widefield microscopy (Reunala et al, 2021; Zone et al, 1996). Transglutaminase (TG) 3 is the known target for dermal IgA in DH, and the majority of DH patients also have circulating TG3 autoantibodies at diagnosis (Sárdy et al, 2002). Despite TG2 being the primary autoantigen in CeD, a subset of patients with CeD also present with serum TG3 antibodies, and it has been hypothesized that these patients might be at risk of future development of DH if gluten-free diet adherence is suboptimal (Kemppainen et al, 2021).

Despite being characteristic for DH, a few studies have presented dermal IgA in patients with CeD without DH (Antiga et al, 2021; Bonciolini et al, 2019; Cannistraci et al, 2007; Seah et al, 1972). This IgA has been reported to be granular, but evidence about its colocalization with TG3 has been contradictory (Antiga et al, 2021; Bonciolini et al, 2019; Cannistraci et al, 2007). These reports raise questions whether the dermal IgA deposits are truly DH specific, and if not, are the deposits detected outside DH identical to those found in DH. Hence, this study aimed to investigate the occurrence of dermal IgA deposits in DH risk groups, that is, patients with CeD and the first-degree relatives (FDRs) of patients with DH/CeD and to further evaluate its colocalization with TG3.

The study included 17 patients with CeD (10 untreated and 7 on gluten-free diet) and 65 FDRs and, as controls, 16 untreated DH and 37 dermatological patients (Table 1). All participants underwent dermatological investigations, with skin punch biopsies investigated for dermal IgA with widefield DIF and a subset of biopsies also with confocal DIF for IgA and TG3 (detailed study protocol is provided in Supplementary Materials and Methods). Furthermore, serological and genetic analysis were performed.

In DIF widefield microscopy with anti-IgA antibody from DAKO, routinely used in diagnostics, dermal granular IgA deposition was detected in the skin biopsy of 1 patient with CeD and 1 FDR (Figure 1a and c). All the remaining 80 study participants showed no such deposits, and by definition, all DH controls were dermal IgA positive, and all dermatological controls were negative. For confocal DIF microscopy, samples were additionally stained for IgA with an antibody (Thermo Fisher Scientific) allowing double staining for TG3. The patient with CeD with positive dermal IgA was found to be inconsistent in the degree of positivity between different anti-IgA antibodies and sections in confocal evaluation (Figure 1a), whereas the FDR did not show clear dermal IgA positivity (Figure 1c). Furthermore, the IgA did not colocalize with TG3 in either participant. All other biopsies from CeD, FDRs, and dermatological controls were clearly dermal IgA deposition negative, and TG3 was not detected at dermal–epidermal junctions (Supplementary Figure S1). All DH controls had dermal IgA deposition that colocalized with TG3 (Supplementary Figure S1c).

Neither the patient with CeD nor the FDR with suggestive dermal IgA positivity in widefield DIF had past or present skin symptoms. Both had CeD/DH compatible HLA DQ haplotypes but were negative for serum TG2 and endomysial antibodies. Serum TG3 antibodies of the dermal IgA–positive patient with CeD were borderline positive (17.3 AU/ml), and those of the dermal IgA positive were FDR negative (6.1 AU/ml). Altogether, 3 dermal IgA–negative study participants (2 patients with CeD and 1 FDR) had positive TG3 antibodies (Table 1). A commercially available TG3 antibody ELISA kit and an "in-house" TG3 antibody ELISA assay (Ziberna et al, 2021) (Supplementary Materials and Methods) gave parallel results (Supplementary Figure S2).

During follow-up of the patient with CeD and FDR with suggestive dermal IgA positivity, the dermal IgA positivity seen in widefield microscopy disappeared at the first follow-up skin biopsy from the patient with CeD (gluten-free diet duration of 1.3 years), whereas it remained positive throughout the whole 3-year follow-up for the FDR on a gluten-containing diet (Figure 1b and d). However, in confocal microscopy, neither granular pattern nor TG3 colocalization was detected. Both participants were serum TG2 and TG3 antibody and endomysial antibody negative during follow-up.

Abbreviations: CeD, celiac disease; DH, dermatitis herpetiformis; DIF, direct immunofluorescence; FDR, first-degree relative; TG, transglutaminase

Accepted manuscript published online XXX; corrected proof published online XXX

Table 1. Background Data and Results of Study Patients and Controls

	Study Patients		Controls	
Study Data	**Patients with CeD, n = 17**	**FDRs, n = 65**	**DH controls, n = 16**	**Dermatological controls, n = 37**
Age, y, median (range)	50 (25–67)	48 (18–74)	46 (20–76)	39 (20–69)
Females, n (%)	11 (65)	48 (74)	6 (38)	29 (78)
Adherence to GFD, n (%)				
Strict	6 (35)	0 (0)	0 (0)	0 (0)
Dietary lapses	1 (6)	0 (0)	0 (0)	0 (0)
Normal gluten-containing diet	10 (59)	65 (100)	16 (100)	37 (100)
GFD duration, y, median[1] (range)	5 (0.3-16)	-	-	-
Serum TG2 antibody positive[2], n (%)	10 (59)	0 (0)	10 (63)	1 (3)
Serum EmA positive[3], n (%)	9 (53)	0 (0)	9 (56)	0 (0)
Serum, TG3 antibody positive[4], n (%)	2 (11.7)	1 (1.5)	9 (57)	0 (0)
Serum TG3 antibody levels, median (IQR)	7 (6.4)	8.7 (2.8)	26.5 (29.8)	7 (4.0)
DIF widefield IgA positive, n (%)	1 (5.8)	1 (1.5)	16 (100)	0 (0)
DIF confocal IgA positive[5], n (%)	1/14 (7.1)	1/58 (1.7)	14/14 (100)	0/4 (0)
DIF confocal IgA/TG3 colocalization[5], n (%)	0/14 (0)	0/58 (0)	14/14 (100)	0/4 (0)
DH/CeD-type HLA[6], n (%)	17 (100)	45 (69)	16 (100)	18 (49)
Current skin symptoms, n (%)	4 (24)[7]	23 (35)[7]	16 (100)	35 (95)[7]
Current abdominal symptoms[8], n (%)	13 (76)	46 (71)	12 (75)	24 (65)
Thyroid disease, n (%)	3 (18)	11 (17)	1 (6)	6 (16)
Diabetes mellitus type 1, n (%)	0 (0)	1 (2)	0 (0)	0 (0)

Abbreviations: CeD, celiac disease; BMI, body mass index; DH, dermatitis herpetiformis; DIF, direct immunofluorescence; EmA, endomysial antibody; FDR, first-degree relative; GFD, gluten-free diet; TG, transglutaminase.
[1]Only participants adhering to GFD included (n = 7).
[2]Greater than 7 U/l considered positive.
[3]1: ≥5 and 1: ≥10 titers considered positive when using respectively human umbilical cord and monkey esophagus as antigens.
[4]Greater than 22 AU/ml considered positive.
[5]Confocal DIF was carried out in a subset of patients with available samples.
[6]HLA-DQ2 and/or HLA-DQ8 positive.
[7]All had non-DH–type skin symptoms.
[8]Diarrhea, vomiting, stomach pain, constipation, and flatulence.

In this study investigating the occurrence of dermal IgA deposition in DH risk groups, it was established that dermal IgA deposition outside DH is a rare phenomenon. Importantly, colocalization of IgA and TG3 was not detected in such cases, indicating that the deposits might be unspecific. Of note, 41% of our patients with CeD were on gluten-free diet, which might at least partly explain the lower occurrence of dermal IgA in CeD than reported in earlier studies comprising untreated patients with CeD (Antiga et al, 2021; Bonciolini et al, 2019; Cannistraci et al, 2007). Furthermore, the CeD cohort size was relatively small in this study, and only 3 non-DH individuals were serum TG3 antibody positive, which may influence the findings. Moreover, it is not excluded that partly differing anatomical skin biopsy sampling sites between the studies might contribute to inconsistency of the findings.

To our knowledge, this study demonstrates a previously unreported dermal IgA depositions that is detected in an FDR who, interestingly, had HLA DQ compatible with DH/CeD but did not develop DH or any other symptoms or signs of CeD during follow-up. Furthermore, also in this case, colocalization with TG3 was lacking. It is generally accepted that dermal IgA deposition in DH targets and thus colocalizes with TG3, but there is currently insufficient knowledge of the origins, target, or clinical implications of dermal IgA deposits in the absence of TG3 colocalization. Furthermore, the significance of dermal IgA deposition in the absence of clinical manifestations compatible with DH is unknown, and without further evidence, it should not be considered a marker of DH or CeD. TG3–IgA double stain is useful and encouraged in challenging situations because it can provide additional information and confirmation as to whether the findings could be related to DH.

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki, and it was approved by the Regional Medical Research Ethics Committee of the Wellbeing Services County of Pirkanmaa (R17042 and R17043). All participants provided written informed consent to participate in this study.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available on request from the corresponding author TS (teea.salmi@tuni.fi). The data are not publicly available owing to the Finnish legislation concerning patient-related data.

KEYWORDS

Celiac disease; Colocalization; Dermatitis herpetiformis; Ig A; transglutaminase 3

ORCIDs

Elli Turjanmaa: http://orcid.org/0000-0001-8548-7708
Helka Kaunisto: http://orcid.org/0000-0002-4038-0816
Esko Kemppainen: http://orcid.org/0000-0002-5491-5391
Noora Nilsson: http://orcid.org/0000-0001-9608-5923

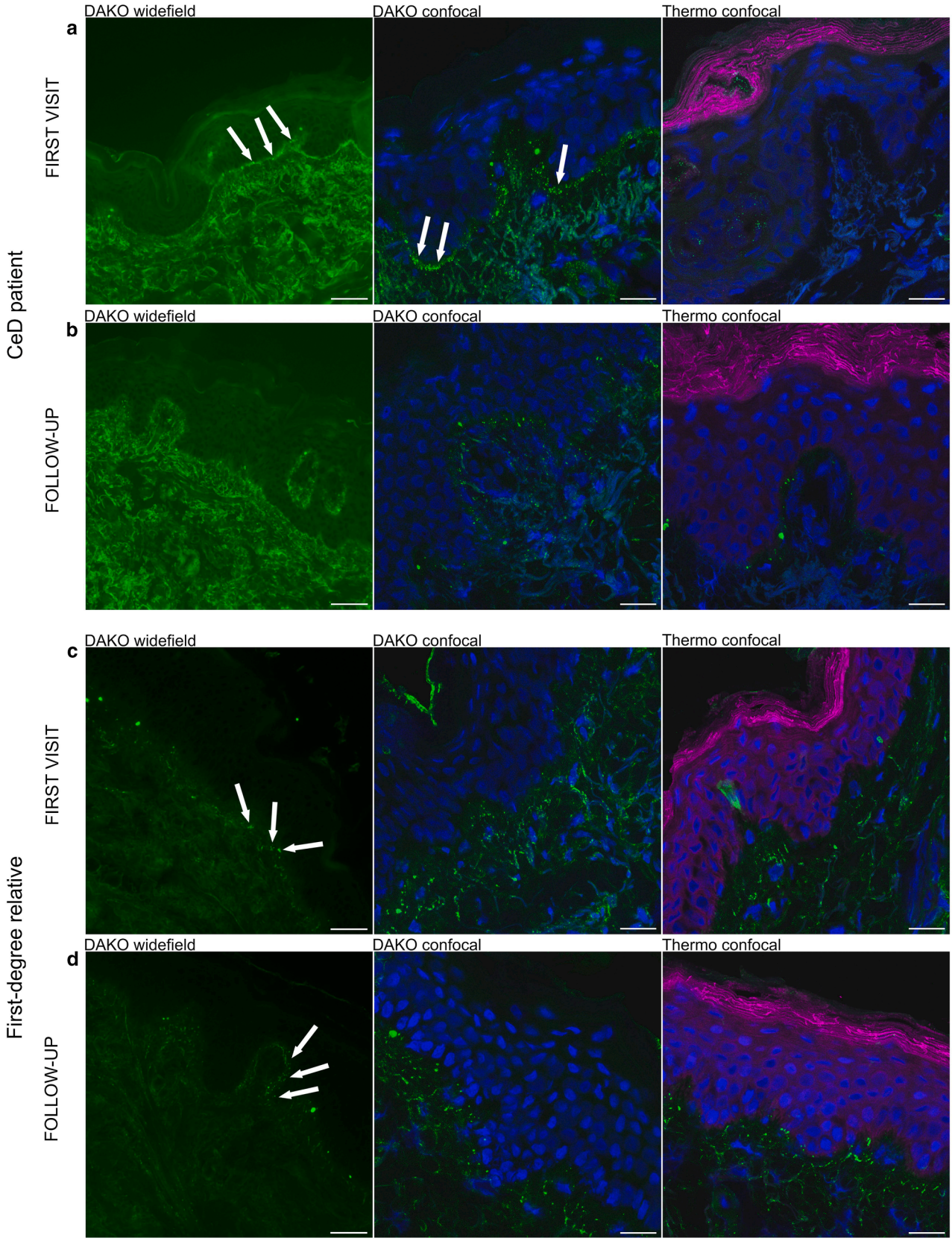


Figure 1. Comparative direct immunofluorescence images of dermal IgA deposition in participants with CeD and FDR with suggestive IgA deposition, taken with widefield or confocal microscope using different anti-IgA antibodies. (**a**–**d**) Composed of ×20 magnification (left) taken on widefield microscope and stained with DAKO anti-IgA and ×40 magnification of serial sections stained with DAKO anti-IgA (middle) or Thermo Fisher Scientific anti-IgA (right) imaged with confocal microscope. (**a**) First visit and (**b**) first follow-up visit of the patient with CeD; (**c**) first visit and (**d**) second follow-up visit of the FDR. Green stain is IgA, blue stain is nuclei, and magenta stain is TG3. TG3 staining was only done in combination with Thermo anti-IgA. IgA positivity is highlighted with white arrows. Bar in widefield images = 50 μm and 20 μm in confocal images. CeD, celiac disease; FDR, first-degree relative; TG3, transglutaminase 3.

Kaisa Hervonen: http://orcid.org/0000-0002-6759-8399
Juha Jernman: http://orcid.org/0000-0002-5927-962X
Päivi Saavalainen: http://orcid.org/0000-0002-1399-1689
Johanna Lempainen: http://orcid.org/0000-0001-9893-1468
Anna Alakoski: http://orcid.org/0000-0003-3760-0109
Luigina De Leo: http://orcid.org/0000-0003-4013-1630
Fabiana Ziberna: http://orcid.org/0000-0002-9748-902X
Timo Reunala: http://orcid.org/0000-0002-6271-5189
Katri Kaukinen: http://orcid.org/0000-0002-5046-8133
Katri Lindfors: http://orcid.org/0000-0001-7417-5151
Teea Salmi: http://orcid.org/0000-0001-7459-4938

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The authors acknowledge Biocenter Finland and Tampere Imaging Facility for providing the confocal microscope and image analysis software. This study was financially supported by the Finnish Coeliac Society, the Finnish Dermatological Society, Tampere University Hospital, the Allergy Research Foundation, the Finnish Cultural Foundation Pirkanmaa Regional Fund, Tampere University Hospital Support Foundation (grant T64084), the State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grants T64084, T66834, T66364, and T62834), the Research Council of Finland (grants 339183, 347471, and 347473), and the Sigrid Jusélius Foundation. This study has been presented as an abstract at the Annual Meeting of European Society for Dermatological Research in 2024 and Tampere Celiac Disease Symposium in 2025. This research was conducted in Tampere, Finland.

AUTHOR CONTRBUTIONS

Conceptualization: ET, HK, EK, KK, KL, TS; Data Curation: ET, HK, EK, NN, KH, AA, KK, KL, TS; Formal Analysis: ET, HK, EK, KK, KL, TS; Funding Acquisition: KL, KK, TS; Investigation: ET, HK, EK, NN, KH, IM, JJ, PS, JL, AA, TR, KK, KL, TS; Methodology: ET, HK, EK, PS, JL, LDL, FZ, KK, KL, TS; Project Administration: EK, KL, KK, TS; Resources: EK, NN, KH, AA, KK, KL, TS; Supervision: EK, KL, KK, TS; Validation: ET, HK, EK, KK, KL, TS; Visualization: ET, HK, EK, KK, KL, TS; Writing - Original Draft Preparation: ET, HK, EK, KK, KL, TS; Writing - Review and Editing: ET, HK, EK, NN, KH, IM, JJ, PS, JL, AA, LDL, FZ, TR, KK, KL, TS

Disclaimer

The funding sources had no role in the design, conduct, analysis, or result interpretation of the study or manuscript preparation or approval.

Elli Turjanmaa[1,2,8], Helka Kaunisto[2,8], Esko Kemppainen[2], Noora Nilsson[1,2], Kaisa Hervonen[1,2], Iida Mankki[2], Juha Jernman[3], Päivi Saavalainen[4], Johanna Lempainen[5], Anna Alakoski[1], Luigina De Leo[6], Fabiana Ziberna[6], Timo Reunala[2], Katri Kaukinen[2,7], Katri Lindfors[2] and Teea Salmi[1,2,*]

[1]Department of Dermatology, Tampere University Hospital, Wellbeing Services County of Pirkanmaa, Tampere, Finland; [2]Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere, Finland; [3]Fimlab Laboratories, Pathology Department, Tampere, Finland; [4]Folkhälsan Research Centre and Faculty of Medicine, Helsinki, Finland; [5]Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland; [6]Institute for Maternal and Child Health, I.R.C.C.S. "Burlo Garofolo", Trieste, Italy; and [7]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

[8]These authors contributed equally to this work.

[*]Corresponding author e-mail: teea.salmi@tuni.fi

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at 10.1016/j.jid.2025.09.380.

REFERENCES

Antiga E, Maglie R, Lami G, Tozzi A, Bonciolini V, Calella F, et al. Granular deposits of IgA in the skin of coeliac patients without dermatitis herpetiformis: a prospective multicentric analysis. Acta Derm Venereol 2021;101:adv00382.

Bonciolini V, Antiga E, Bianchi B, Del Bianco E, Ninci A, Maio V, et al. Granular IgA deposits in the skin of patients with coeliac disease: is it always dermatitis herpetiformis? Acta Derm Venereol 2019;99:78–83.

Cannistraci C, Lesnoni La Parola I, Cardinali G, Bolasco G, Aspite N, Stigliano V, et al. Co-localization of IgA and TG3 on healthy skin of coeliac patients. J Eur Acad Dermatol Venereol 2007;21:509–14.

Kemppainen E, Salmi T, Lindfors K. Missing insight into T and B cell responses in dermatitis herpetiformis. Front Immunol 2021;12:657280.

Reunala T, Hervonen K, Salmi T. Dermatitis herpetiformis: an update on diagnosis and management. Am J Clin Dermatol 2021;22:329–38.

Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med 2002;195:747–57.

Seah PP, Fry L, Stewart JS, Chapman BL, Hoffbrand AV, Holborow EJ. Immunoglobulins in the skin in dermatitis herpetiformis and coeliac disease. Lancet 1972;1:611–4.

Ziberna F, Sblattero D, Lega S, Stefani C, Dal Ferro M, Marano F, et al. A novel quantitative ELISA as accurate and reproducible tool to detect epidermal transglutaminase antibodies in patients with Dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2021;35:e78–80.

Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol 1996;132:912–8.

SUPPLEMENTARY MATERIALS AND METHODS

Patients and study protocol

This study was conducted at the Department of Dermatology, Tampere University Hospital and at the Celiac Disease Research Center, Tampere University (Tampere, Finland). The study groups consisted of 17 patients with celiac disease (CeD) and 65 first-degree relatives, whereas the positive control group was formed by 16 dermatitis herpetiformis (DH) controls, and the negative control group was formed by 37 dermatological controls. All study participants were at least aged 18 years.

Seven patients with a prior diagnosis of CeD and all 65 first-degree relatives were a subgroup of participants participating in a CeD family study between 2018 and 2021 (Paavola et al, 2022). Ten additional untreated patients with CeD diagnosed between 2017 and 2020 were also included. In all 17 study patients with CeD, the diagnosis was small bowel biopsy proven, and at diagnosis, 76% suffered from classical gastrointestinal symptoms, 18% suffered from extraintestinal symptoms of CeD, whereas 6% were asymptomatic and found by screening of CeD risk groups, for example, the first-degree relatives of patients with CeD and DH and patients with autoimmune diseases such as type 1 diabetes mellitus. The control groups comprised patients originally referred between 2017 and 2022 to the Department of Dermatology owing to suspicion of DH. Of these patients, 16 were diagnosed with DH on the basis of typical clinical picture and detection of granular dermal IgA deposits with direct immunofluorescence (DIF) using widefield microscopy and thus constituted the DH control group. Villous atrophy was detected in 7 of 11 (64%) DH controls undergoing gastroscopy and small bowel biopsy investigations, and 3 of 4 without villous atrophy were further investigated, and all had CeD-type inflammation in the small bowel. The remaining 36 patients constituted the dermatological control group because they were excluded for DH on the basis of clinical dermatological investigation together with absence of dermal IgA deposits in DIF examination. These patients were found to have eczema (42%), folliculitis (22%), granuloma annulare (8%), lichenoid dermatitis (6%), psoriasis (3%), dermographismus (3%), and erythema multiforme (3%), and altogether, 13% had unspecific dermatitis.

All study patients and controls were interviewed by a study nurse or a dermatologist specialized in DH/CeD about their long-term illnesses and possible adherence to and duration of gluten-free diet and clinical symptoms. In addition, patients with CeD were asked about the time of their CeD diagnosis and the preceding symptoms. At the same visit, blood samples were taken from all study patients and controls for CeD antibody measurements and HLA typing (described in detail below).

Moreover, all study participants underwent detailed dermatological investigations. The subgroup of patients from the CeD family study were investigated by a dermatologist a median of 7 months (range = 0−42 months) after the study nurse's interview, and all other patients underwent all examinations at the same visit. In the dermatological investigation, patients and controls were asked about past or present skin diseases diagnosed by a medical doctor. Their skin was examined clinically, and a skin punch biopsy was taken. The biopsy was taken from healthy skin on the elbow from patients without any skin findings because this is the most common location for DH rash (Antiga et al, 2019), and recommended biopsy site in DH is predilection site (Görög et al, 2021). In patients presenting with skin symptoms, the biopsy was taken from the perilesional skin of the elbow, knee, buttock, abdomen, or scalp to avoid false-negative results (Zone et al, 1996). The biopsies were thereafter investigated for dermal IgA with DIF (in detail below), and in those study patients with dermal IgA deposition detected in widefield microscopy, annual follow-up for up to 3 years was arranged with clinical investigation, CeD antibody measurements, and skin biopsies with dermal IgA examination with DIF.

The study protocol adheres to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the regional Ethics Committee of Tampere University Hospital (R17042 and R17043). All study participants gave their written informed consent.

Serology and HLA haplotyping

Serum endomysial antibodies titers were measured as described before (Ladinser et al, 1994) using human umbilical cord (or monkey esophagus) as an antigen and considering titers $\geq$1:5 ($\geq$1:10) positive. A commercial fluorescence enzyme immunoassay (Celikey, Phadia) was used to determine serum transglutaminase 2 antibody (IgA) levels, applying a cut off >7 U/l for seropositivity. Serum transglutaminase 3 antibody (IgA) levels were determined using both a commercial assay (Immunodiagnostik) with a cut off <16 for seronegativity and >22 for seropositivity and an "in-house" method developed by Ziberna et al (2021), with a minor modification using commercial positive and negative control samples from the Immunodiagnostik assay to enable cross-validation of the results between the 2 methods.

Genotyping for the CeD risk-associated HLA haplotypes was performed on whole blood samples using qPCR-based tagging SNP approach as described elsewhere (Kiviniemi et al, 2007; Koskinen et al, 2009).

Histology and image acquisition

All dermal biopsies from patients with CeD, first-degree relatives, and DH and dermatological controls were investigated for IgA deposition in widefield microscopy using DIF with FITC-conjugated anti-IgA (number 760-2681, Roche Diagnostics or by DAKO) as a part of routine diagnostic practice by an experienced dermatopathologist. For confocal microscopy, DIF transglutaminase 3/IgA double staining with FITC-conjugated anti-transglutaminase 3 (A030, Zedira) and tetramethylrhodamine-conjugated anti-IgA (A18786, Thermo Fisher Scientific) were performed as described before (Hietikko et al, 2018).

Imaging with Zeiss LSM 800 Laser Scanning Confocal Microscope was carried out with the following set-up: images of biopsies were collected in z-plane with ×40 magnification, air immersion, and 0.37-μm step size. Pinhole size was set at 44 μm for all tracks, laser

strength used was maximum 1%, and detector gain maximum of 800V and minimum of 500 V. The confocal assessment was done in a blinded manner. In cases of discrepancy between the confocal and widefield results, a further evaluator with dermatological expertise was consulted.

Raw image files collected by the confocal microscope were deconvoluted using Huygens Essential software (version 23.10) using standard settings, with the exception of setting the signal-to-noise ratio to 5 and the quality change threshold to 0.001. Fiji-ImageJ software (version 2.14.0) was used for merging and assigning pseudo colors to the deconvoluted images as well as addition of bars. For the confocal images in Figure 1, brightness and contrast were adjusted using the levels function in GNU Image Manipulation Program. No manipulation of brightness or contrast was carried out for other images. Images obtained from widefield microscope were cropped to fit a cubic ratio.

SUPPLEMENTARY REFERENCES

Antiga E, Bonciolini V, Cazzaniga S, Alaibac M, Calabrò AS, Cardinali C, et al. Female patients with dermatitis herpetiformis show a reduced diagnostic delay and have higher sensitivity rates at autoantibody testing for celiac disease. BioMed Res Int 2019;2019:6307035.

Görög A, Antiga E, Caproni M, Cianchini G, De D, Dmochowski M, et al. S2k guidelines (consensus statement) for diagnosis and therapy of dermatitis herpetiformis initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2021;35:1251–77.

Hietikko M, Hervonen K, Salmi T, Ilus T, Zone JJ, Kaukinen K, et al. Disappearance of epidermal transglutaminase and IgA deposits from the papillary dermis of patients with dermatitis herpetiformis after a long-term gluten-free diet. Br J Dermatol 2018;178:e198–201.

Kiviniemi M, Hermann R, Nurmi J, Ziegler AG, Knip M, Simell O, et al. A high-throughput population screening system for the estimation of genetic risk for type 1 diabetes: an application for the TEDDY (the Environmental Determinants of Diabetes in the Young) study. Diabetes Technol Ther 2007;9:460–72.

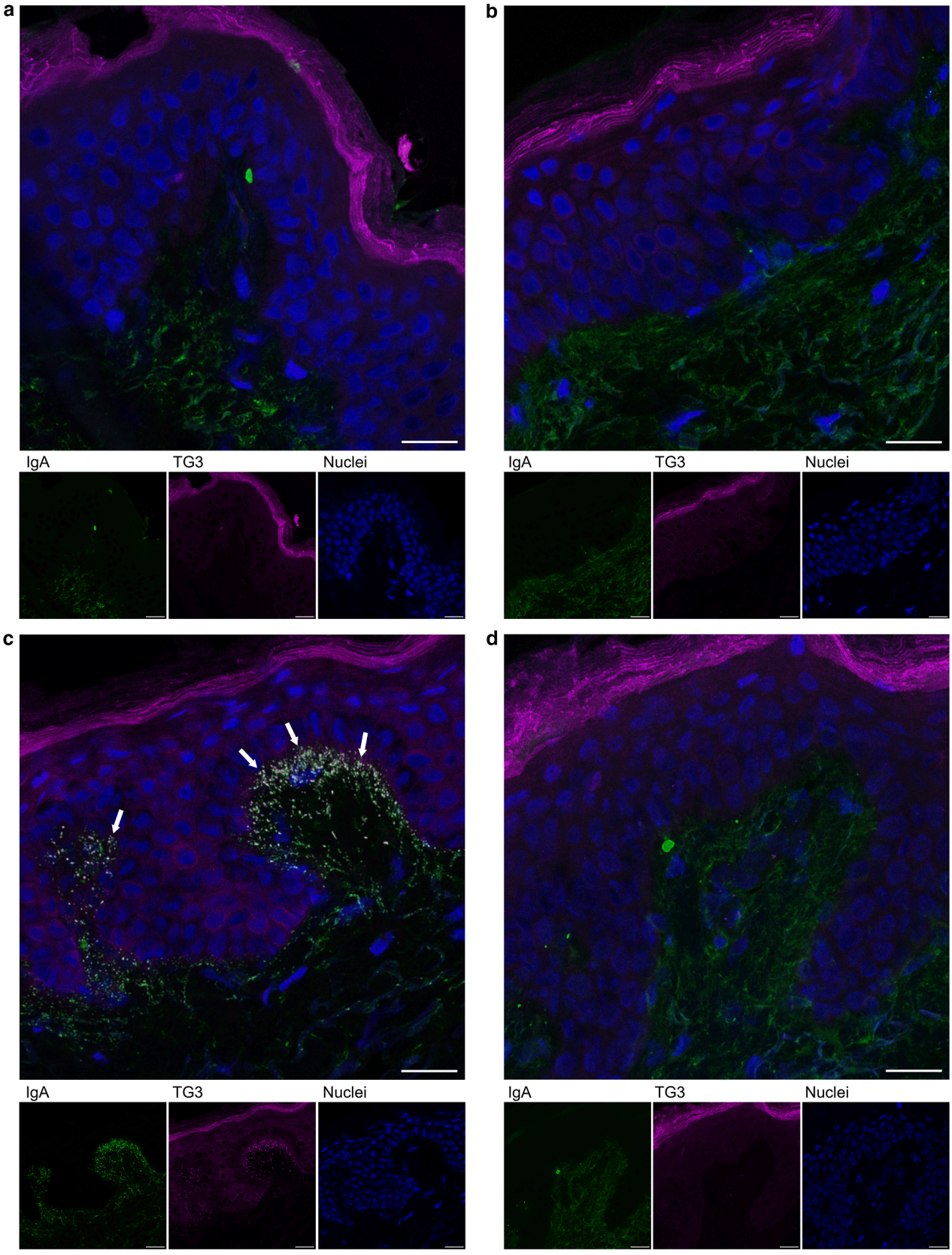
Koskinen L, Romanos J, Kaukinen K, Mustalahti K, Korponay-Szabo I, Barisani D, et al. Cost-effective HLA typing with tagging SNPs predicts celiac disease risk haplotypes in the Finnish, Hungarian, and Italian populations. Immunogenetics 2009;61:247–56.

Ladinser B, Rossipal E, Pittschieler K. Endomysium antibodies in coeliac disease: an improved method. Gut 1994;35:776–8.

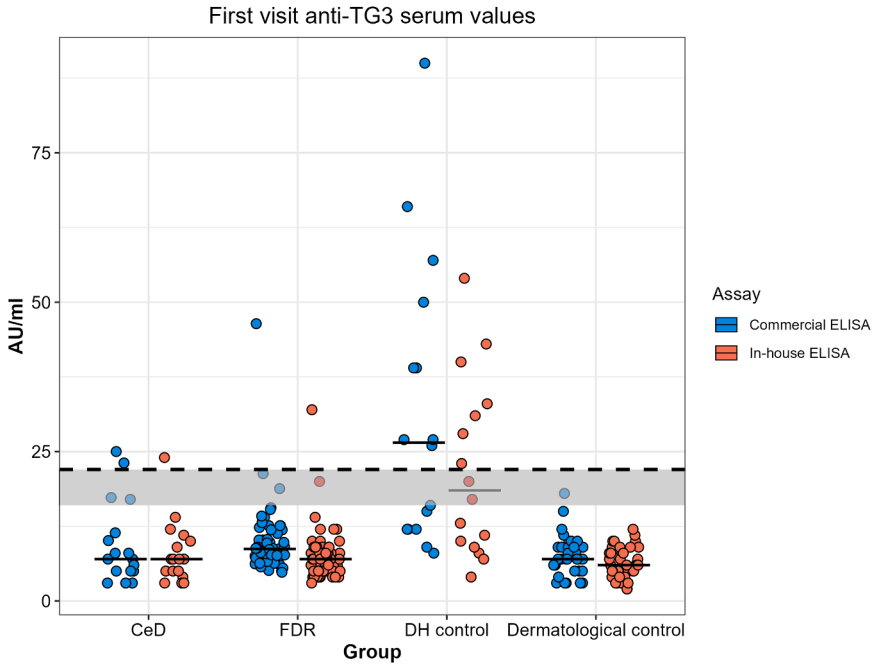
Paavola S, Kurppa K, Huhtala H, Saavalainen P, Lindfors K, Kaukinen K. Coeliac disease re-screening among once seronegative at-risk relatives: a long-term follow-up study. United European Gastroenterol J 2022;10:585–93.

Ziberna F, Sblattero D, Lega S, Stefani C, Dal Ferro M, Marano F, et al. A novel quantitative ELISA as accurate and reproducible tool to detect epidermal transglutaminase antibodies in patients with Dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2021;35:e78–80.

Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol 1996;132:912–8.



Supplementary Figure S1. Representative confocal direct immunofluorescence images of each study and control group. **(a)** Celiac disease study patient, (**b**) first-degree relative, (**c**) dermatitis herpetiformis control, and (**d**) dermatological control. Panels **a**–**d** consist of a merged image of all 3 stains, with individual stains depicted below the merged image. Each sample was stained with Thermo anti-IgA (green), anti-TG3 (magenta), and DAPI for nuclei (blue). IgA and TG3 colocalization appear in white. IgA deposition is highlighted with white arrows. Bar = 20 μm. TG3, transglutaminase 3.



Supplementary Figure S2. Serum transglutaminase 3 antibody values for study patients and controls using commercial (Immundiagnostik, blue color) and in-house (red color) ELISA methods. Broken line indicates positive cut off value (22 AU/ml), and gray area borderline indicates positive values (16–21 AU/ml) in the commercial ELISA quantification. Horizontal bars indicate medians. AU, arbitrary unit; CeD, celiac disease; FDR, first-degree relative; DH, dermatitis herpetiformis.