Brief report

A novel *CARD11* heterozygous missense variant in a CADINS patient

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Background: ***CARD11*-associated atopy with dominant interference of NF-κB signaling (CADINS) is developed as a result of heterozygous loss-of-function variants in *CARD11* that function as strong dominant-negative alleles. In lymphocytes, *CARD11* encodes a scaffold protein that links activation of the antigen receptor with downstream signaling. Patients with CADINS generally experience severe atopic dermatitis, asthma, recurrent pneumonia and other upper respiratory tract infections, skin infections, and allergies to a variety of dietary and environmental antigens. Additionally, patients experience elevated levels of serum IgE, but low to normal levels of other immunoglobulin types.**

Objective: We performed genetic diagnosis of a patient of nonconsanguineous descent presenting at 11 years of age with severe atopic dermatitis, asthma, food allergy, skin and recurrent infections, and an extremely elevated level of serum IgE.

Methods: We performed whole genome sequencing of samples obtained from the patient and his entire family.

Results: Clinical, laboratory, genetic, and functional findings suggested CADINS. Genetic evaluation revealed a novel heterozygous missense variant (c.2913C>G, p.Cys971Trp) in the *CARD11* gene as the potential underlying defect. Expression of *CARD11* variant–stimulated constitutive NF-κB activity in T-cell lines demonstrated both loss-of-function and dominant-negative activity.

Conclusion: A novel germline heterozygous missense variant (c.2913C>G) in *CARD11* potentially leads to CADINS. (J Allergy Clin Immunol Global 2025;4:100461.)

Key words: CARD11, *CADINS, eczema, asthma, food allergies, loss-of-function variant, dominant negative, heterozygous variant, atopic dermatitis, CBM complex*

Abbreviations used

AD:	Atopic dermatitis
CADINS:	*CARD11*-associated atopy with dominant interference of NF-κB signaling
CARD11:	Caspase activation and recruitment domain family member 11
DN:	Dominant negative
EH:	Eczema herpeticum
GOF:	Gain of function
HSV:	Herpes simplex virus
LOF:	Loss of function
NF-κB:	Nuclear factor kappa–light-chain enhancer of activated B cells

INTRODUCTION

Germline mutations in the caspase activation and recruitment domain family member 11 *(CARD11)* gene lead to at least 3 kinds of primary immunodeficiency: *CARD11*-associated atopy with dominant interference of nuclear factor kappa–light-chain enhancer of activated B cells (NF-κB) signaling, or CADINS, which is due to heterozygous loss-of-function (LOF) dominant-negative (DN) mutations; B-cell expansion with NF-κB and T-cell anergy (aka BENTA) due to heterozygous gain-of-function (GOF) mutations; and homozygous LOF mutations leading to *CARD11* deficiency. Despite all 3 syndromes' shared susceptibility to infections, only CADINS has a high rate of atopy and diverse clinical manifestations, which vary from patient to patient.[1-6] CARD11 is a key protein scaffold with 1154 amino acids that connects antigen detection and downstream NF-κB activation in lymphocytes.[7] It plays a crucial role as a signal transducer for T and B lymphocytes, transferring information from the cell surface antigen receptor to the cytoplasmic IκB kinase (aka IKK), which then activates the conventional NF-κB pathway.[8] It is also known as CARMA1 and consists of N-terminal caspase recruitment domain (CARD,

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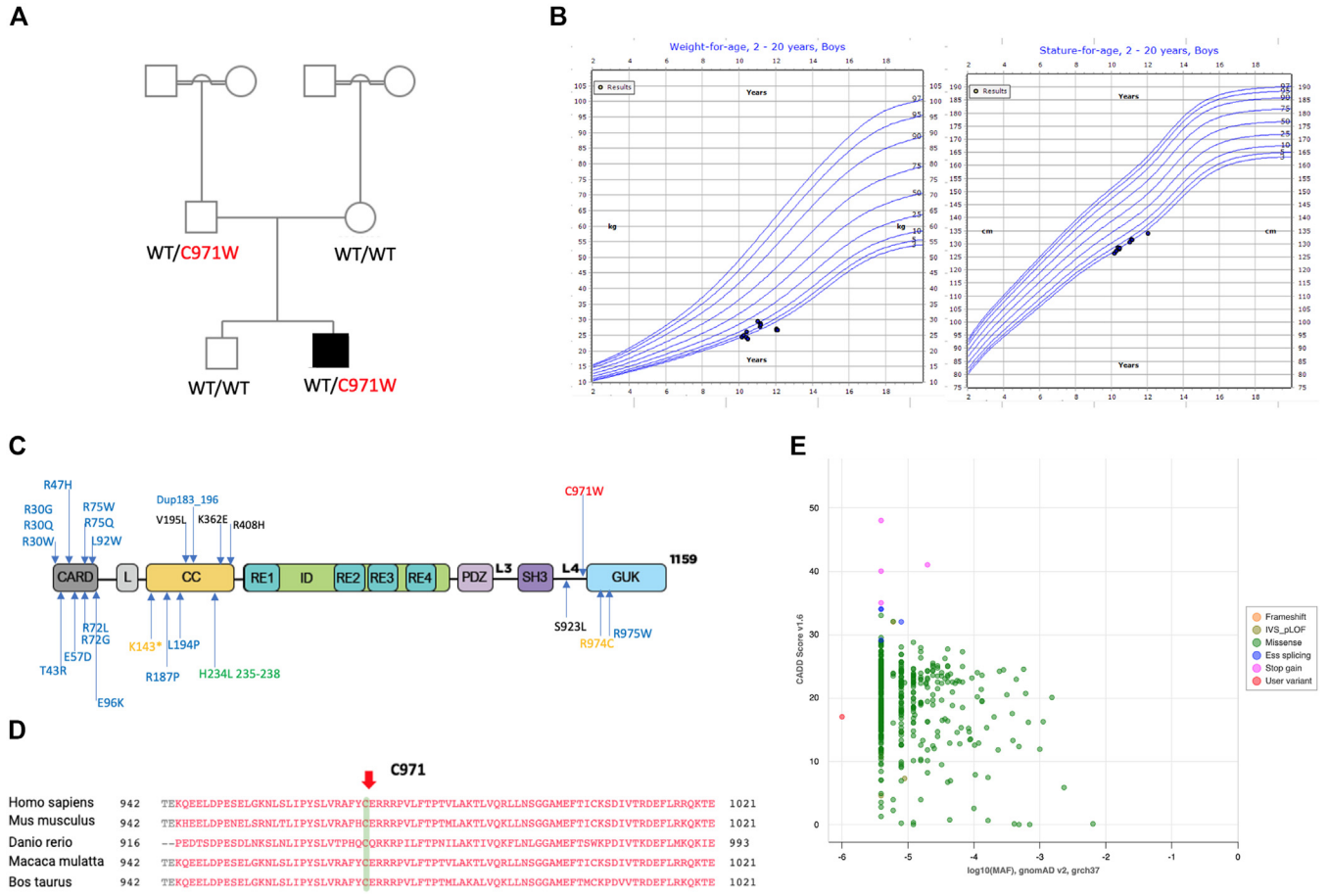


FIG 1. Clinical phenotype and genotype of patient. **(A)** Family pedigree shows affected patient with *black square.* **(B)** CDC growth charts for patient's height (ages 5-19) and body surface area (ages 2-20). **(C)** CARD11 protein diagram highlights novel C971W variant *(red)* compared to known LOF variants *(black)* and DN variants *(blue/orange).* **(D)** C971 residue in CARD11 is highly conserved across species. **(E)** MAF versus CADD scores for *CARD11* variants using gnomAD data (gnomad.broadinstitute.org). *CADD,* Combined annotation-dependent depletion; *CDC,* Centers for Disease Control and Prevention; *MAF,* minor allele frequency.

1-110), LATCH (112-130), and coiled-coil (CC, 130-449) domains and C-terminal membrane–associated guanylate kinase domain (MAGUK, 667-1140), which is made up of PDZ, SH3, and GUK domains.[3]

CADINS, which was first reported in 2017, is defined by atopy and a variety of autoimmune and/or infectious symptoms. It has been demonstrated that heterozygous LOF *CARD11* mutations, which function as strong DN alleles, are the underlying genetic cause of this condition.[9] In the past few years, it has been shown that autosomal-dominant hyper-IgE syndrome with atopy and hypogammaglobulinemia is driven by heterozygous LOF, DN mutations in the *CARD11* gene; it has also been referred to as immunodeficiency 11B with atopic dermatitis (AD) (MIM 617638).[10] Because of the accompanying B- and/or T-cell defects, the majority of CADINS patients experienced a more severe infectious phenotype than those with only classical AD.[11] The signs and symptoms of CADINS, which can include atopic disorders like asthma and allergies, autoimmune diseases, and infections such as in respiratory tract and viral skin infections, are frequently present in people with AD, but they can also differ among relatives and even within families.[10] These clinical signs may be linked to immunologic defects including neutropenia, hypogammaglobulinemia, or aberrant T-cell proliferation and differentiation.[2]

Here we report the finding of a germline heterozygous missense mutation (C971W) in an affected patient in the gene *CARD11* with the associated clinical and immunologic phenotype, which included extreme elevation of serum IgE associated with infections of lung and skin and severe food allergy.

Written informed assent/consent was obtained from the patient and his family members in accordance with protocols approved by the institutional review board at Sidra Medicine. More detailed methods are available in the Methods section in this article's Online Repository.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Sidra Medicine institutional review board (IRB1511001953).

RESULTS AND DISCUSSION

We report a case of suspected CADINS disease in an 11-year-old boy (Fig 1, *A*). The patient, who was of nonconsanguineous descent, exhibited severe AD, unusually high serum IgE levels, and recurrent infections. His father's family had a history of

TABLE I. Key laboratory findings

Clinical test	Value	Reference range
IgG (g/L)	15.61 g/L	2.80-14.80 g/L
IgA (g/L)	1.1 g/L	0.10-1.29 g/L
IgM (g/L)	0.45 g/L	0.12-1.25 g/L
IgE (kU_A/L)	7906 kU_A/L	2-34 kU_A/L
Neutrophils	3.4 × 10^9/L	1.63-7.55 × 10^9/L
Lymphocytes	1.7 × 10^9/L	0.97-3.96 × 10^9/L
Monocytes	0.5 × 10^9/L	0.10-1.10 × 10^9/L
Eosinophils	0.6 × 10^9/L	0-0.70 × 10^9/L
Basophils	0 × 10^9/L	0-0.20 × 10^9/L
CD3	72.8%	52.0-78.0%
CD3 absolute count	1234 cells/μL	800-3500 cells/μL
$CD3^+/CD4^+$	27.8%	25.0-48.0%
$CD3^+/CD4^+$ absolute count	474 cells/μL	400-2100 cells/μL
$CD3^+/CD8^+$	34.9%	9.0-35.0%
$CD3^+/CD8^+$ absolute count	592.00 cells/μL	200-1200 cells/μL
CD19	16.1%	18.0-24.0%
CD19 absolute count	273 cells/μL	200-600 cells/μL
$CD3^-/CD16^+/CD56^+$	10%	6.0-27.0%
$CD3^-/CD16^+/CD56^+$ absolute count	169 cells/μL	70-1200 cells/μL
CD4/CD8 ratio	0.8	~1.5-2.0

TABLE II. Allergen-specific test results

Allergen-specific IgE test (ImmunoCAP)	Serum IgE (kU_A/L)	Grade
Allergen: Almond	>100.00	6
Allergen: *Aspergillus fumigatus*	9.28	3
Allergen: Bermuda grass	23.80	4
Allergen: Brazil nut	27.60	4
Allergen: Cashew	>100.00	6
Allergen: Chickpea	88.80	5
Allergen: Cockroach American	0.90	2
Allergen: Cockroach German	2.36	2
Allergen: Coconut	84.70	5
Allergen: Cod	0.35	1
Allergen: Egg	>100.00	6
Allergen: Hazelnut	44.30	4
Allergen: House dust mix	Positive	NA
Allergen: House dust mite	>100.00	6
Allergen: Cow's milk	>100.00	6
Allergen: Mold mix	Positive	NA
Allergen: Peanut	81.80	5
rAra h 1	12.31	3
rAra h 2	2.75	2
rAra h 3	30.30	4
rAra h 9 LTP	0.79	2
rAra h 8 PR-10	1.07	2
Pistachio	>100.00	6
Allergen: Salmon	1.18	2
Allergen: Sesame seed	>100.00	6
Allergen: Shrimp	42.50	4
Allergen: Soybean	16.40	3
Allergen: Tuna	2.72	2
Allergen: Walnut	23.80	4
Allergen: Wheat	51.40	5
Feather mix (ex72)	Positive	NA

NA, Not applicable.

eczema. The patient's medical history included colitis with fever, asthma, food allergies, poor appetite, and failure to thrive. His first episode of diarrhea occurred at 3 months of age and was due to *Norovirus* gastroenteritis, which persisted until 8 months of age, when blood was observed in his stool. After an upper and lower gastrointestinal endoscopy and evidence of colitis found via gut biopsy, combined with a histologic examination showing bloody stool as well as laboratory findings that included elevated IgE levels, the diagnosis of allergic colitis was confirmed. The patient was treated with prednisolone for 3 months. His diarrhea resolved after therapy with steroids, with bowel movements tending toward constipation.

The patient's serum IgE levels, as shown in Table I, were found to be significantly elevated (>5000 IU/mL; reference range, 2-34 IU/mL), strongly suggesting severe allergic sensitization. IgG and IgA levels are slightly elevated but still within or close to the upper limit of the reference range. At the age of 10 years, the patient experienced anaphylaxis after consuming a small amount of diluted egg white, which may have contributed to his food aversion and failure to thrive. His weight and height were on the 10th and third percentiles for his age, respectively (Fig 1, *B*). He was diagnosed with multiple food allergies, including all tested nuts, cow's milk, eggs, and sesame seeds, as well as environmental allergens including molds, feathers, and house dust mites, and was advised to carry an epinephrine autoinjector (Table II). Other foods, such as legumes and cod, were found to be serum IgE positive but were tolerated without inducing symptoms. The patient's eosinophil count was elevated (0.6-0.7 × 10^9/L; reference range, 0-0.7 × 10^9/L), consistent with the patient's atopic condition. In contrast, other cell types (neutrophils, lymphocytes, monocytes) were within reference ranges. The CD4/CD8 ratio was decreased (0.8; reference range, ~1.5-2.0), and $CD19^+$ B cells were slightly below the reference range (16.1%; reference range, 18.0-24.0%) (Table I). Other T-cell subset counts and CD3/CD4 and CD3/CD8 ratios were within reference ranges, as were numbers of natural killer cells (Table I).

The patient had a history of folliculitis with severe AD, which was treated with topical antibiotics. His severe eczema, present since infancy, partially responded to extensive treatment, including topical steroids and tacrolimus. His condition showed some improvement with wet wrap therapy and beach swimming. His severe eczema herpeticum (EH) was first noted at 6 weeks of age, concentrated mainly in his face, before spreading to include trunk and limbs. He also had a left inferior plaque lens opacity and mild allergic conjunctivitis, with severe ocular surface disease. His eyes showed dryness and staining with fluorescein on wide areas of the conjunctiva and cornea, especially inferiorly. He had bilateral white cataracts, with the left denser than the right. Additionally, he had very mild attacks of asthma, which were treated with fluticasone propionate 125 μg via metered dose inhaler, 2 puffs twice a day, and salbutamol via metered dose inhaler, 2 puffs every 4 hours as needed. Salbutamol was recommended as required for episodes of wheeze.

After whole genome sequencing of samples from the patient, his sibling, and both parents, we identified a novel heterozygous missense variant (c.2913C>G, p.Cys971Trp) in *CARD11* (NM_032415) in both the patient and the father (Fig 1, *C*). In parallel, custom primary immunodeficiency panel sequencing also identified the *CARD11*:p.Cys971Trp variant in the patient; the Sherloc framework was utilized to classify it as a variant of uncertain significance. The affected amino acid is highly conserved in

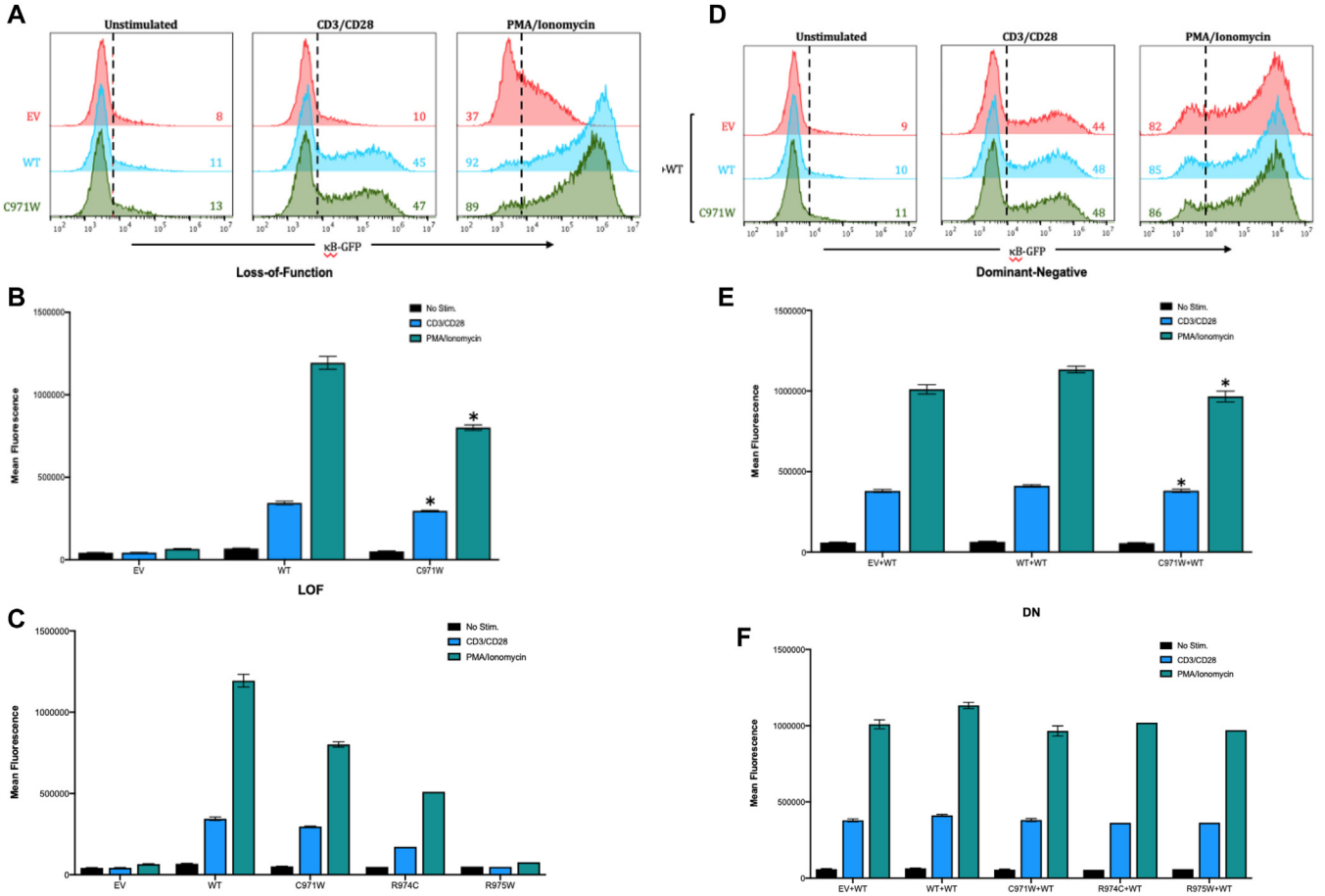
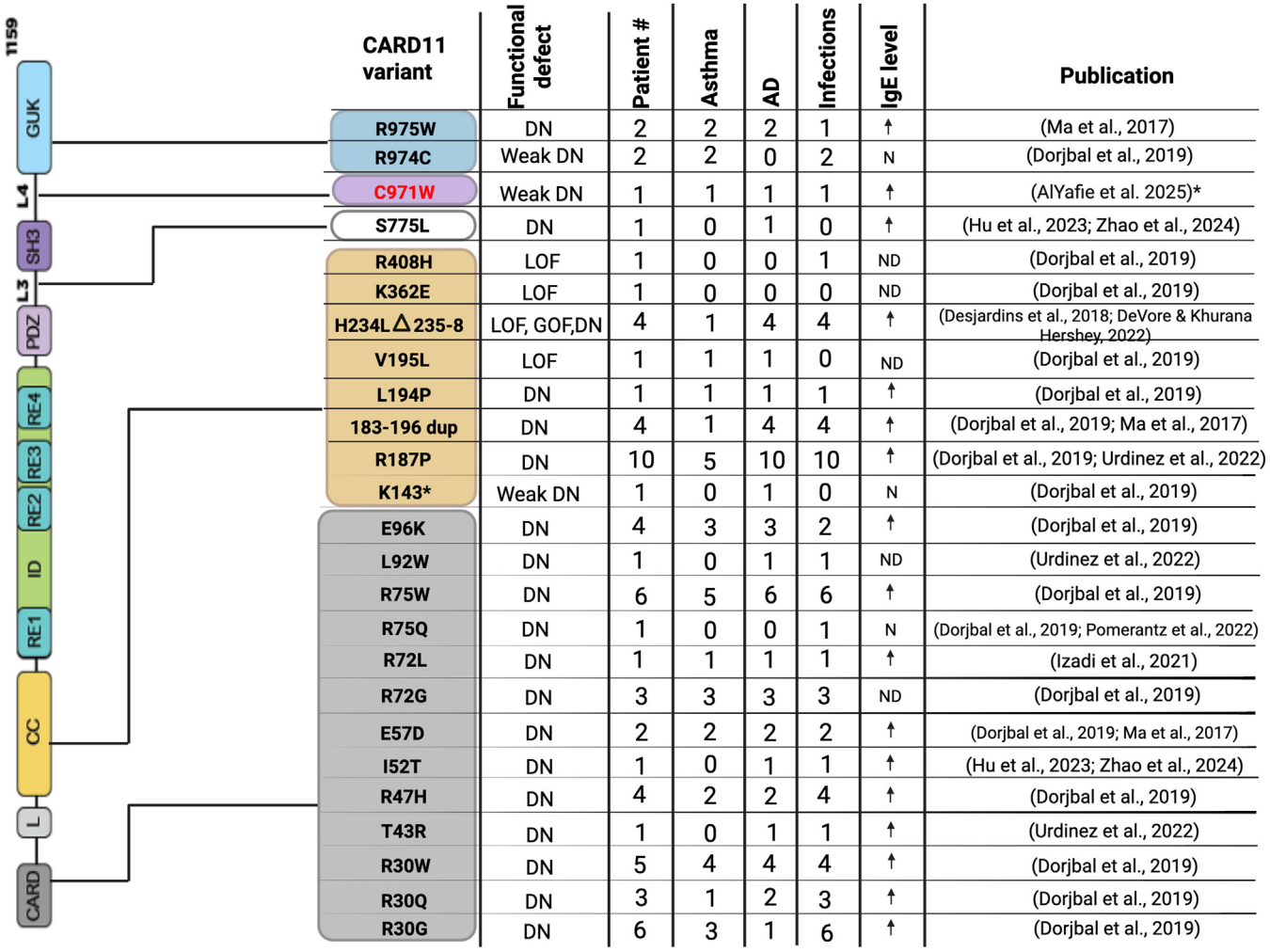


FIG 2. C971W is LOF *CARD11* variant with mild DN activity. **(A)** Flow cytometry shows NF-κB–driven GFP reporter expression in CARD11-deficient JPM506 cells, which were transfected with different CARD11 constructs and subjected to stimulation with CD3/CD28 or PMA/ionomycin. **(B)** LOF assay indicates lower GFP MFI in C971W-transfected cells compared to WT, indicating statistical significance ($P < .05$). **(C)** Immunoblotting confirms CARD11-Flag expression, with β-actin used as loading control. **(D)** Flow cytometry of cells transfected with WT or C971W constructs shows GFP expression after stimulation. **(E)** DN assay shows slight MFI reduction in cells transfected with C971W + WT versus WT + WT. **(F)** Immunoblot verifies CARD11-Flag expression. *GFP,* Green fluorescent protein; *MFI,* mean fluorescence intensity; *PMA,* phorbol 12-myristate 13-acetate; *WT,* wild type.

several vertebrate species, including nonmammalian species such as *Danio rerio* (zebrafish), which further supports a potential functional and/or structural role (Fig 1, *D*). The variant was absent in population datasets, including gnomAD (Fig 1, *E*), ExAC, and 1000 Genomes. Autosomal-dominant inheritance was suggested because the patient and his father were both heterozygous, whereas the mother and the younger sibling showed a homozygous reference genotype. Several computational algorithms predicted the potential effect of this missense change as "deleterious" or "possibly damaging." Although the CADD score, at about 22, was below the mutation significance cutoff for *CARD11,* it was found to be potentially deleterious by functional assays (Fig 2). Using a Jurkat reporter cell model, the variant was shown to result in a partial LOF and a weak DN effect (Fig 2). Additional experimental evaluation of the hypomorphic variant was not possible because of the unavailability of suitable biologic samples, and the patient could not be followed up for further investigation for logistical reasons.

Previous reports indicate that a broadly atopic disease phenotype, presenting in infancy as AD, in conjunction with allergic rhinitis, asthma, food allergies, and even eosinophilic colitis, is common to most CADINS patients.[3] The markedly elevated IgE levels and broad sensitization to both food and environmental allergens point to a hyperactive immune response typical of AD and food allergies. Clinically, the patient exhibited severe dry skin with facial eczematous rashes, and itchy scars. Generally, herpes simplex virus (HSV) infection leads to EH in individuals with AD.[12] Early identification of EH is critical because functional and/or life-threatening issues may arise, with HSV keratitis or keratoconjunctivitis leading to blindness.[12,13] The patient experienced bilateral acute conjunctivitis as a consequence of HSV infection. Importantly, despite the moderately hypomorphic effect of the variant in a Jurkat reporter cell model, total serum IgE was hyperelevated in our patient, reaching >5000 kU_A/L at two separate clinical visits (Table I). A direct link between reduced activity of the CARD11-BCL10-MALT1 complex, known as the CBM complex, and IgE-related allergic conditions has been identified in several studies. In the Japanese population, *CARD11* was found to be a risk locus for AD by a genome-wide association study.[14]



CARD11 variant	Functional defect	Patient #	Asthma	AD	Infections	IgE level	Publication
R975W	DN	2	2	2	1	↑	(Ma et al., 2017)
R974C	Weak DN	2	2	0	2	N	(Dorjbal et al., 2019)
C971W	Weak DN	1	1	1	1	↑	(AlYafie et al. 2025)*
S775L	DN	1	0	1	0	↑	(Hu et al., 2023; Zhao et al., 2024)
R408H	LOF	1	0	0	1	ND	(Dorjbal et al., 2019)
K362E	LOF	1	0	0	0	ND	(Dorjbal et al., 2019)
H234LΔ235-8	LOF, GOF,DN	4	1	4	4	↑	(Desjardins et al., 2018; DeVore & Khurana Hershey, 2022)
V195L	LOF	1	1	1	0	ND	(Dorjbal et al., 2019)
L194P	DN	1	1	1	1	↑	(Dorjbal et al., 2019)
183-196 dup	DN	4	1	4	4	↑	(Dorjbal et al., 2019; Ma et al., 2017)
R187P	DN	10	5	10	10	↑	(Dorjbal et al., 2019; Urdinez et al., 2022)
K143*	Weak DN	1	0	1	0	N	(Dorjbal et al., 2019)
E96K	DN	4	3	3	2	↑	(Dorjbal et al., 2019)
L92W	DN	1	0	1	1	ND	(Urdinez et al., 2022)
R75W	DN	6	5	6	6	↑	(Dorjbal et al., 2019)
R75Q	DN	1	0	0	1	N	(Dorjbal et al., 2019; Pomerantz et al., 2022)
R72L	DN	1	1	1	1	↑	(Izadi et al., 2021)
R72G	DN	3	3	3	3	ND	(Dorjbal et al., 2019)
E57D	DN	2	2	2	2	↑	(Dorjbal et al., 2019; Ma et al., 2017)
I52T	DN	1	0	1	1	↑	(Hu et al., 2023; Zhao et al., 2024)
R47H	DN	4	2	2	4	↑	(Dorjbal et al., 2019)
T43R	DN	1	0	1	1	↑	(Urdinez et al., 2022)
R30W	DN	5	4	4	4	↑	(Dorjbal et al., 2019)
R30Q	DN	3	1	2	3	↑	(Dorjbal et al., 2019)
R30G	DN	6	3	1	6	↑	(Dorjbal et al., 2019)

FIG 3. Comparison of *CARD11* C971W mutation with 23 other CADINS mutations from published case reports. *Left, Colored bars* represent CARD11 protein domains. *CARD11* mutations are clustered in *colored bars* that reflect their location in CARD11 domains. Reported functional defect for CADINS mutations were DN, LOF, GOF, and weak DN. Because asthma, AD, and infections are critical clinical phenotypes associated with CADINS, number of reported cases is listed under each phenotype; 0 indicates absence of clinical phenotype for specific mutation. IgE serum levels are indicated as follows: ↑, high; *N,* normal levels, *ND,* not determined. *Refers to this report.

CARD11 is required for antigen receptor–induced NF-κB activation and lymphocyte proliferation.[15] The amino acid affected in our case is located just upstream of a putative guanylate kinase–like domain (positions 973-1140) and is in close proximity to previously reported DN mutations (R974C, R975W) implicated in CADINS disease.[3] The patient's low CD4/CD8 ratio suggested a relative reduction in helper T-cell function compared to cytotoxic T cells, often seen in immune dysregulation, while the slight decrease in $CD19^+$ B cells may correlate with immune modulation in atopy. The presence of eosinophilia further supports a CADINS diagnosis because it reflects chronic allergic inflammation.

We conducted a literature search and reviewed the 9 articles identified published from 2014 to 2024 with the keywords "CADINS" and "CARD11" in PubMed, Medline, and Clinvar. Because "CADINS" is a new term that initially was described in 2018, we also searched using the keywords "severe atopic disease" and "CARD11." A total of 67 CADINS patients in 29 families, with 24 different heterozygous germline *CARD11* variants, were identified (Fig 3). Eighteen of the *CARD11* germline variants have been reported as having a DN effect. While K143*, R974C,[3] and C971W (from this study) exhibit a relatively weak DN effect, V195L, K362E, and R408H have been documented as only LOF mutations because there was no observed DN activity associated with them.[3] H234L 235-238 represents a distinctive heterozygous germline indel mutation within the *CARD11* gene. This mutation is notable for combining pathogenic characteristics of both LOF and GOF mutations, making it a unique and complex variant.[16]

CADINS is a primary immunodeficiency disorder that can present any of a broad spectrum of clinical manifestations with incomplete penetrance. Severe allergic manifestations were noted in patients with CADINS—for instance, approximately 76% were distinguished with AD and 57% with asthma. Recurrent bacterial and viral infections were also more common in CADINS patients, mainly pneumonias (62%) and molluscum contagiosum (55%). Warts and cutaneous HSV type 1 were also recognized in some patients. Serum IgE titers are typically extremely high in the majority of CADINS cases, which predispose those individuals to

allergic hypersensitivities, although in some cases the IgE serum levels were not determined. Other clinical sequelae can include food allergy, failure to thrive, allergic rhinitis, bronchiectasis, autoimmunity (eg, alopecia), eosinophilic colitis, and neutropenia. R75W is the only mutation that has been reported with CADINS clinical phenotype as well as two different malignancies: a human papillomavirus–driven anal squamous cell carcinoma and skin-infiltrating T-cell lymphoma.[10] Although pathogenic variants are more likely to occur in the N-terminal CARD and CC domains, it remains challenging to predict exact genotype–phenotype relationships solely on the basis of the location of variants within CARD11 domains; additional research is needed to link heterozygous variants with specific clinical characteristics.

In summary, we identified a novel variant in the *CARD11* gene that is potentially responsible for initiation of the patient's CADINS and could expand the phenotypic spectrum further to include EH-related ocular disease. Given that the father carries the same variant, further investigation of factors either present or absent in the father would be useful to fully evaluate the variant's effect. Because other genetic or environmental factors may be involved, careful examination of independent cases with similar variants will be needed to further substantiate the pathogenic role of the *CARD11* (c.2913C>G) variant and its impact on CBM complex–dependent downstream signaling and lymphocyte function.

DISCLOSURE STATEMENT

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Clinical implications: A novel heterozygous missense variant (c.2913C>G) in *CARD11* potentially leads to the development of CADINS in a patient of nonconsanguineous descent presenting with severe AD, asthma, food allergy, skin, and recurrent infections as well as extremely elevated levels of serum IgE.

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