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Brief Communication

Expression in *Escherichia coli* and Purification of Folded rDer p 20, the Arginine Kinase From *Dermatophagoides pteronyssinus*: A Possible Biomarker for Allergic Asthma

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ABSTRACT

Arginine kinase (AK) was first identified as an allergen in the Indian-meal moth and subsequently shown to occur as allergen in various invertebrates and shellfish. The cDNA coding for AK from the house dust mite (HDM) species *Dermatophagoides pteronyssinus*, Der p 20, has been isolated, but no recombinant Der p 20 (rDer p 20) allergen has been produced and characterized so far. We report the expression of Der p 20 as recombinant protein in *Escherichia coli*. rDer p 20 was purified and shown to be a monomeric, folded protein by size exclusion chromatography and circular dichroism spectroscopy, respectively. Using AK-specific antibodies, Der p 20 was found to occur mainly in HDM bodies, but not in fecal particles. Thirty percent of clinically well-characterized HDM allergic patients (n = 98) whose immunoglobulin E (IgE) reactivity profiles had been determined with an extensive panel of purified HDM allergens (Der f 1, 2; Der p 1, 2, 4, 5, 7, 10, 11, 14, 15, 18, 21, 23 and 37) showed IgE reactivity to Der p 20. IgE reactivity to Der p 20 was more frequently associated with lung symptoms. AKs were detected in several invertebrates with specific antibodies and Der p 20 showed IgE cross-reactivity with AK from shrimp (*Litopenaeus vannamei*). Thus, Der p 20 is a cross-reactive HDM allergen and may serve as a diagnostic marker for HDM-induced lung symptoms such as asthma.

Keywords: *Escherichia coli*; allergy and immunology; house dust mites; Der p 20 arginine kinase; recombinant allergen; allergic asthma; IgE; biomarker; allergy diagnosis

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INTRODUCTION

Arginine kinase (AK) was first identified as an allergen in the Indian-meal moth (*Plodia interpunctella*) which is a frequent household pest in many countries.[1,2] Screening of a *P. interpunctella* expression cDNA library with serum immunoglobulin E (IgE) from an Indian-meal moth-sensitized allergic patient led to the isolation of a cDNA coding for AK. A recombinant AK from Indian-meal moth, Plo i 1,had been expressed and shown to react specifically with IgE from sensitized patients and to induce IgE-dependent basophil activation and skin reactions.[1] Furthermore, IgE cross-reactivity with house dust mite (HDM), cockroach and shellfish had been demonstrated. AKs are involved in cellular energy homeostasis in the muscles of invertebrates where they catalyze the transfer of phosphate between phosphoarginine and adenosine diphosphate to provide adenosine triphosphate for muscle contraction.[3] Like tropomyosins, AKs have later been described as possible cross-reactive allergens, including *Dermatophagoides farinae,* in many invertebrates such as crustaceans, mollusks, insects and arachnids.[1,4-13] In many cases, HDM extracts strongly inhibited IgE binding to various cross-reactive allergen sources, but no significant inhibition was shown *vice versa*, suggesting HDM as primary sensitizing agent.[14-18]

The HDM species *Dermatophagoides pteronyssinus* is one of the most important allergen sources worldwide containing several allergens in the body and fecal pellets[19] of which Der p 1, Der p 2, Der p 5, Der p 7, Der p 21 and Der p 23 have been identified as the clinically most relevant allergens.[20] The cDNA coding for Der p 20, the AK from *D. pteronyssinus*, has been isolated (GenBank: EU684970.1), but so far no recombinant Der p 20 (rDer p 20) has been expressed, purified and characterized regarding physiochemical and immunological properties, and possible clinical relevance. In this study, we report the expression and immunological characterization of Der p 20 and investigate its potential relevance as a biomarker for allergic asthma.

MATERIALS AND METHODS

Details of Materials and Methods are provided in **Supplementary Data S1**.

Patients with HDM allergy

Study participants (n = 98) suffering from HDM-induced allergy symptoms were enrolled and characterized as described (52.9% females, mean age 24.9 ± 4.7 years).[21] Symptoms and IgE-sensitization to other HDM allergens were assessed by a questionnaire and allergen microarray, respectively. Total nasal symptom scores were obtained during controlled exposure to HDM-allergens in the Vienna Challenge Chamber. Approval of the study was obtained from the Clinical Pharmacology Ethics Committee (03/12) (Vienna, Austria).

Expression, purification and biochemical analysis of rDer p 20

The cDNA sequence of Der p 20 (GenBank: EU684970.1) with a DNA sequence coding for a C-terminal hexahistidine tag was ligated into pET-17b. After transformation into *Escherichia coli* BL21 (DE3), protein expression was induced by isopropyl β-D-1-thiogalactopyranoside (IPTG). Expression levels and localization of the target protein within the host cells were determined by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) (not shown). The protein was purified from the supernatant of *E. coli* lysate by nickel chelate affinity chromatography under native conditions. Secondary structure and oligomerization were determined by circular dichroism (CD)-spectroscopy and size-exclusion

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chromatography, respectively. Sequences of other AKs with homology to Der p 20 were identified by comparing the amino acid sequence of Der p 20 with the sequences deposited in the UniProt database (www.uniprot.org/blast/) using the BLASTP program.

IgE-binding frequencies and association with clinical phenotypes

IgE binding to Der p 20 was determined in patients' sera by enzyme-linked immunosorbent assay (ELISA). Differences concerning patterns of sensitization to other HDM allergens, clinical symptoms, additional allergies and sensitizations were statistically evaluated and compared between Der p 20-positive and -negative patients (see **Supplementary Fig. S1**).

Identification of AK in extracts from different invertebrates and inhibition assays

Extracts were prepared from specimens of different mite species (*D. pteronyssinus* and *farinae*, *Blomia tropicalis*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*), cockroach (*Periplaneta americana*, *Blattella germanica*) and from Pacific white shrimp (*Litopenaeus vannamei*). Extracts were blotted onto a nitrocellulose membrane and the presence of AK was investigated using rabbit-antibodies raised against AK from *P. interpunctella* (Indian-meal moth) (Davids Biotechnologie, Regensburg, Germany). Binding of IgG to AK was visualized by autoradiography.

IgE cross-reactivity between Der p 20 and AK from *L. vannamei* was analyzed using serum from a Der p 20-positive patient. This serum was pre-incubated with rDer p 20 and IgE binding to blotted extracts was visualized with ^{125}I-labelled anti-human IgE.

RESULTS

rDer p 20 was purified from the soluble fraction of *E. coli* under non-denaturing conditions with a yield of approximately 2 mg of protein per liter of bacterial culture. Under non-reducing conditions, the protein showed 3 bands on the SDS-PAGE that lay close to each other at a molecular weight of approximately 40 kDa, whereas under reducing conditions only 1 band was visible (**Fig. 1A**). Since the Der p 20 sequence (GenBank accession number: EU684970.1) contains 4 cysteine residues, we hypothesized that the 3 bands are due to correctly (*i.e.*, intramolecular) or partially disulfide-bonded versions as well as versions with only free SH-groups. We therefore investigated the presence of free SH-groups in the rDer p 20 protein preparation by coupling rDer p 20 with the carrier molecule keyhole limpet hemocyanin via SH-groups (**Supplementary Fig. S2**). After coupling, 2 bands with free SH-groups disappeared and 1 containing intramolecular SH-bonds remained (**Supplementary Fig. S2**), supporting our hypothesis.

The analysis of the secondary structure of the protein by far ultraviolet CD spectroscopy revealed 2 minima at 206 and 220 nm, respectively, and a maximum at 194 nm (**Fig. 1B**). Calculations using CDSSTR Software indicated that Der p 20 consists of 32% α-helices, 20% β-strands, 22% turns and 26% random coils. Thus, rDer p 20 is a folded protein exhibiting a mixed alpha helical and beta-sheet secondary structure. The thermal denaturation recorded by CD demonstrated a single melting point at 59°C without refolding upon cooling (data not shown).

Size-exclusion chromatography with Superdex 200 Increase 10/300 column material and multi angle light scattering (MALS) demonstrated that rDer p 20 occurs as a monomeric

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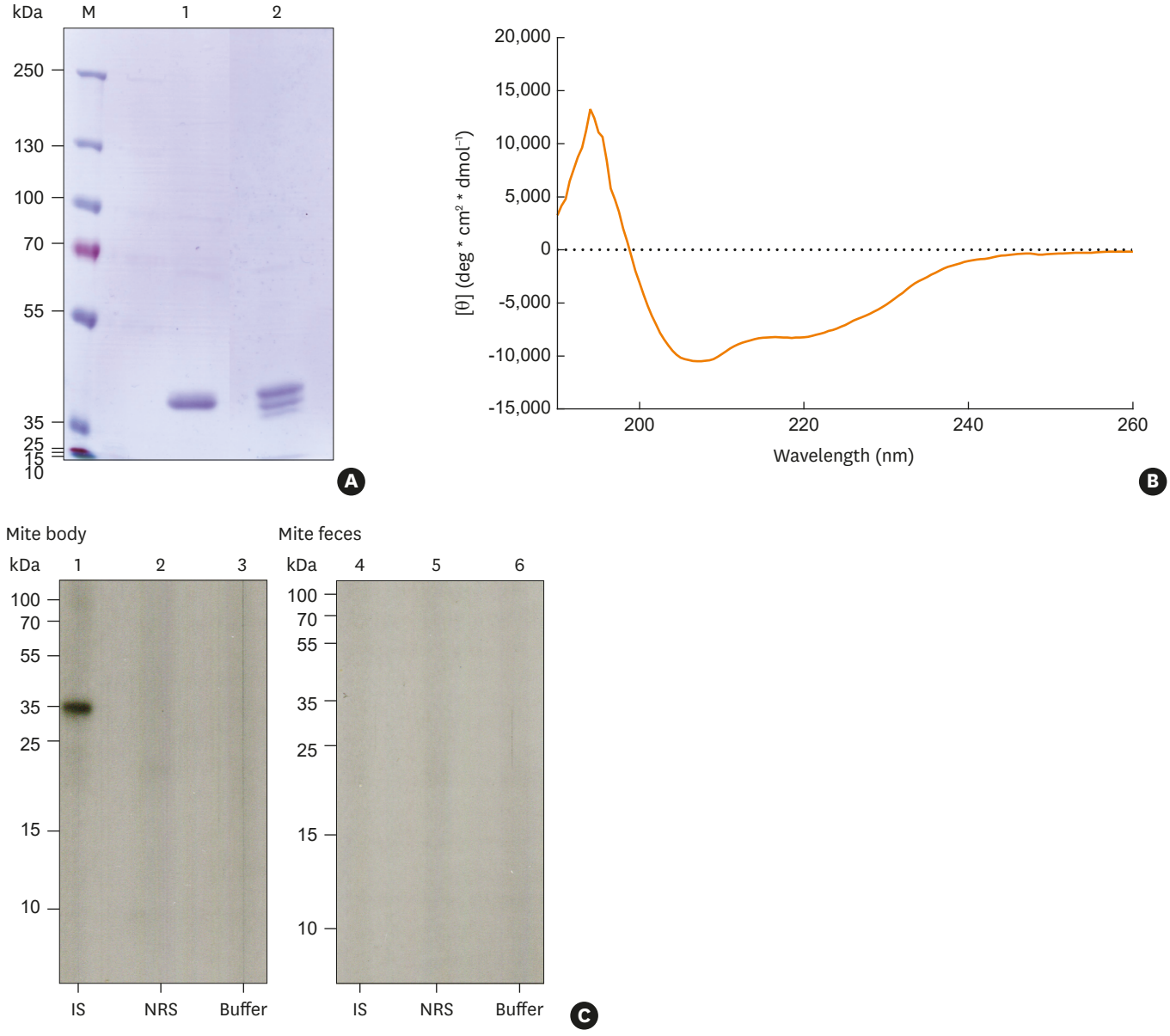

Fig. 1. (A) Coomassie Brilliant Blue-stained sodium dodecyl sulphate-polyacrylamide gel electrophoresis (8%) of 5 μL of purified recombinant Der p 20 (concentration = 0.66 mg/mL) under reducing (lane 1) or non-reducing conditions (lane 2). Lane M: molecular weight marker. (B) Far ultraviolet circular dichroism analysis of recombinant Der p 20. The graph displays molar ellipticities (*y*-axis) recorded at different wavelengths (*x*-axis). (C) Detection of Der p 20 in nitrocellulose-blotted extracts of *Dermatophagoides pteronyssinus* body (left panel) and feces (right panel). The molecular weights in kDa are indicated on the left.
IS, rabbit anti-Plo i 1 immune serum; NRS, normal rabbit pre-immune serum.

protein (**Supplementary Fig. S3**) with a molecular weight of 42 ± 4 kDa as measured by MALS which was in agreement with the molecular weight of 41.3 kDa calculated according to the sequence that included the hexahistidine tag. Using rabbit antibodies specific for Plo i 1, the Der p 20-related AK from the Indian-meal moth, we detected Der p 20 in extracts made from mite bodies, whereas it was not detectable in the mite fecal pellets (**Fig. 1C**).

The equivalence of rDer p 20 and natural Der p 20 regarding IgE reactivity was demonstrated by inhibition of serum IgE binding of a patient who was only sensitized to Der p 20 and Der p 2. Pre-incubation of the patient's serum with rDer p 20 completely inhibited IgE reactivity to

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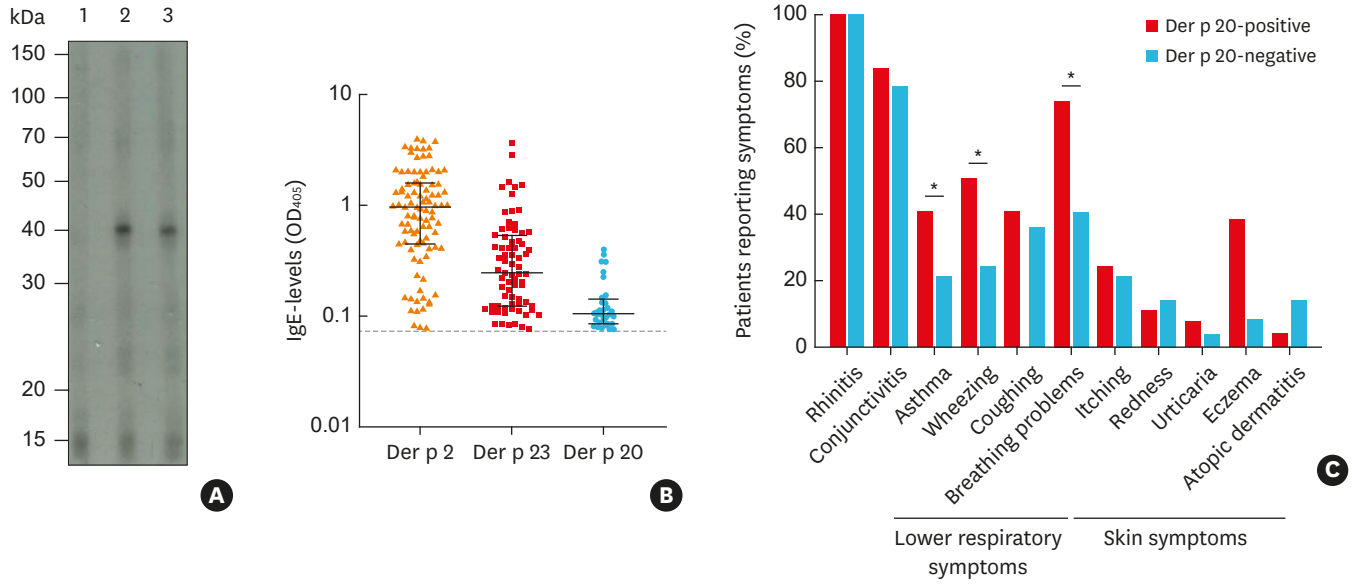

Fig. 2. (A) rDer p 20 inhibits allergic patient's IgE binding to nitrocellulose-blotted extract from *Dermatophagoides pteronyssinus*. Serum from a Der p 20-sensitized patient was pre-incubated with rDer p 20 (lane 1), with human serum albumin (lane 2) or without inhibitor (lane 3). IgE reactivity was detected with ^{125}I-labeled anti-human IgE and visualized by autoradiography. The molecular weights in kDa are indicated on the left. (B) IgE levels determined for Der p 2, Der p 23 and Der p 20 (*x*-axis) for 98 house dust mite allergic patients in one enzyme-linked immunosorbent assay experiment. OD values correspond to bound IgE (*y*-axis, logarithmic scale). The statistical cutoff is indicated by the dashed horizontal line. Error bars indicate medians ± interquartile ranges of OD values from positive patients. (C) Percentages of the 98 patients (*y*-axis) reporting different types of symptoms (*x*-axis) are shown for Der p 20-positive (red bars) and -negative (blue bars) subjects.
IgE, immunoglobulin E; rDer p 20, recombinant Der p 20; OD, optical density.
*Statistically significant differences between the groups are indicated ($P < 0.05$).

natural Der p 20 (40 kDa) in HDM extract, whereas IgE reactivity to Der p 2 (approximately 15 kDa) was not affected (**Fig. 2A**).

Next, we compared the frequency of IgE reactivity to rDer p 20 and Der p 20-specific IgE levels with Der p 2 and Der p 23 in a cohort of clinically well characterized HDM allergic patients (n = 98) in one ELISA experiment. We found that 30 out of 98 patients (*i.e.*, 30.6%) showed specific IgE reactivity to rDer p 20, whereas 99% and 73.5% of the patients showed IgE reactivity to Der p 2 and to Der p 23, respectively. The median level of IgE specific for Der p 20 (optical density [OD] = 0.10) was lower than for Der p 23 (OD = 0.24) and Der p 2 (OD = 0.95) (**Fig. 2B**).

Despite the fact that Der p 20-specific IgE levels were low, we found that significantly higher percentages of Der p 20-sensitized patients reported symptoms of asthma (40% vs. 20.5%, $P = 0.045$), wheezing (50% vs. 23.5%, $P = 0.009$) and overall breathing problems (73.3% vs. 39.7%, $P = 0.002$) as compared to non-Der p 20-sensitized patients (**Fig. 2C** and **Supplementary Table S1**). The observed differences regarding lower respiratory symptoms seemed to be due to Der p 20-sensitization because we found no significant differences regarding sensitization to other common allergen sources such as birch, grass, mugwort/rye pollen and cat/dog dander between Der p 20-positive and -negative patients (data not shown). In contrast to lower respiratory symptoms, rhinitis was not associated with Der p 20 sensitization. Among the 34 rhinitis patients who did not have any lower respiratory symptoms, only 5 were Der p 20-positive, whereas the vast majority (*i.e.*, 29 out of 34) was Der p 20-negative. Among the 72 rhinitis patients without asthma, only 18 were Der p 20-positive and 54 were Der p 20-negative. These findings indicate that Der p 20 is a possible

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marker for HDM-triggered allergic asthma and lower respiratory symptoms. No significant differences were found in reported symptoms of rhinitis, conjunctivitis or skin symptoms (**Fig. 2C**), and there were no significant differences regarding total nasal symptom scores as measured during a controlled exposure to HDM allergens in the Vienna Challenge Chamber (**Supplementary Fig. S1A**).

We also investigated if IgE reactivity to Der p 20 is associated with IgE reactivity to certain other HDM allergens or with IgE reactivity to a certain number of HDM allergens (**Supplementary Fig. S1B-D**), but no such associations were found.

Supplementary Fig. S4 shows that AKs occur in various invertebrates, including mites, spiders, insects, crayfish and shrimps, and that Der p 20 shares high sequence identities (*i.e.*, > 70%) with these AKs. The highest sequence identities were found between Der p 20 and AKs from other mites (*D. farinae*, *Euroglyphus maynei*, *Sarcoptes scabiei* and *Aleuroglyphus ovatus*), whereas the sequence identities with AK from *Amphioctopus fangsiao* and *Apostichopus japonicus* and creatine kinases from vertebrates (*Gallus gallus*, *Mus musculus* and *Homo sapiens*) were lower (*i.e.*, in the range of 40%–50%) (**Supplementary Fig. S4**).

Accordingly, using a rabbit antiserum specific for Plo i 1 we could detect AKs in extracts from different allergen sources (*D. pteronyssinus*, *D. farinae*, *T. putrescentiae*, *P. americana*, *L. vannamei*) (**Supplementary Fig. S5**, left stripes), showing bands at the respective molecular weights of species-specific AKs (40, 40, 43, 40 and 39 kDa, respectively). However, with the rabbit antiserum used, no bands could be detected in extracts from *B. tropicalis, L. destructor* and *B. germanica*. Since the sequence homologies of AKs from mites and cockroach are > 70% (**Supplementary Fig. S4**), it is likely that they were not well represented in the allergen extracts (not shown).

Some IgE cross-reactivity between Der p 20 and the AK of the Pacific shrimp *L. vannamei* was demonstrated by IgE-inhibition experiments. Preincubation of serum from a Der p 20-sensitized patient with rDer p 20 reduced IgE binding to AK in shrimp extract (**Supplementary Fig. S6**, lane 1). However, this patient showed no allergic symptoms upon consumption of shrimps. Likewise, none of the 30 patients sensitized to Der p 20 among the 98 study participants reported symptoms of food allergy.

DISCUSSION

Our study provides new data regarding the prevalence of IgE reactivity and the possible role of Der p 20, *i.e.*, the AK from *D. pteronyssinus,* in HDM allergy. r Der p 20 was expressed in *E. coli* and purified as folded, monomeric protein. IgE immunoblot analysis showed that rDer p 20 inhibits IgE binding to natural Der p 20, indicating that the recombinant allergen may contain the IgE epitopes of the natural protein. Furthermore, we showed that Der p 20 is localized mainly in the body of the mite, but seemed to be absent from fecal pellets. The IgE-recognition frequency of Der p 20 was measured in sera from 98 clinically well characterized HDM-allergic patients by ELISA. We found that 30% of the 98 tested HDM-allergic patients showed IgE reactivity to rDer p 20. Although Der p 20-specific IgE levels were lower as compared to Der p 2- and Der p 23-specific IgE levels, IgE reactivity against Der p 20 was significantly associated with asthma symptoms. In particular, we found that an increased percentage of patients positive to Der p 20 reported breathing problems, in particular asthma and wheezing, whereas no significant

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associations were found with nasal, eye or skin symptoms. This result is in agreement with data found in the literature, where AKs from spider, shellfish or snail were reported to be involved in asthma symptoms. Hence, IgE sensitization to Der p 20 could be a useful serological biomarker or at least an indicator for lower respiratory symptoms.

Unlike previously reported for subjects sensitized to Der p 10 (tropomyosin) where higher sensitization frequencies to other HDM allergens were detected,[22] no significant differences were observed between Der p 20-positive versus -negative patients.

A possible role of AK as a cross-reactive allergen in invertebrates and shellfish was supported by the demonstration of binding of AK-specific rabbit antibodies to AKs from different mites, cockroachand shrimps and by the demonstration that pre-incubation of serum from a Der p 20-sensitized patient with rDer p 20 inhibited IgE binding to shrimp AK. However, this result might be particularly relevant regarding food allergies where linear epitopes play an important role as in immunoblotting conformational epitopes might be lost to a certain extent.

It is a limitation of our study that we could not perform a direct comparison of recombinant Der p 20 with natural Der p 20 because it was difficult to purify sufficient amounts of pure, intact, non-degraded nDer p 20 from house dust mite extracts. However, since rDer p 20 was shown to be a folded protein as demonstrated by CD, we assume that it also contained the relevant conformational epitopes and thus will be suitable for diagnostic purposes.

rDer p 20 can now be used for the diagnosis of HDM allergy and to study cross-reactivity among AKs from invertebrates and shellfish. Importantly, IgE reactivity to Der p 20 may be a serological marker for HDM-associated asthma.

SUPPLEMENTARY MATERIALS

Supplementary Data S1

Details of materials and methods

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Supplementary Table S1

Frequency of symptoms in Der p 20-positive and -negative patients

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Supplementary Fig. S1

(A) TNSSs obtained during controlled HDM-allergen exposure in a challenge chamber are summarized as AUC values (*y*-axis) for Der p 20-positive and -negative subjects (*x*-axis). (B) Percentages of Der p 20-sensitized (red bars) and -non-sensitized (blue bars) patients (*y*-axes) with specific immunoglobulin E to other allergens from *D. farinae* and *D. pteronyssinus* (*x*-axis) and (C) with different numbers of sensitizations to other HDM allergens (*x*-axis). (D) Numbers of sensitization to other HDM allergens (*y*-axis) are shown for individual patients for the Der p 20-positive and -negative groups (*x*-axis). Error bars represent medians ± interquartile ranges.

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Supplementary Fig. S2

Coomassie blue-stained sodium dodecyl sulphate-polyacrylamide gel electrophoresis under non-reducing conditions containing rDer p 20 alone (lane 1), KLH alone (lane 2) and rDer p 20 after coupling to KLH (lane 3). The molecular weights are indicated on the left margin. The gel was run under non-reducing conditions.

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Supplementary Fig. S3

Size exclusion chromatography of rDer p 20. The graph shows the absorbance at 280 nm (*y*-axis) and the elution volumes in ml (*x*-axis). Molecular weights of standard proteins corresponding to the elution volumes given are indicated with black arrows.

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Supplementary Fig. S4

Percentages of amino acid sequence identity between Der p 20 and arginine kinases from other invertebrates. Identities of 60%–70%, > 70%–80% and > 80% (from light to dark orange colors) are highlighted by colored boxes.

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Supplementary Fig. S5

Nitrocellulose-blotted extracts from (1) *Dermatophagoides pteronyssinus*, (2) *Dermatophagoides farinae*, (3) *Periplaneta americana*, (4) *Tyrophagus putrescentiae* and (5) *Litopenaeus vannamei* were probed with rabbit anti-Plo i 1-specific antibodies (left stripes) or for control purposes with buffer alone (right stripes). Bound rabbit IgG was detected with ^{125}I-labelled anti-rabbit IgG and was visualized by autoradiography. The molecular weights in kDa are indicated on the left margins.

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Supplementary Fig. S6

Recombinant Der p 20 inhibits allergic patient's IgE binding to AK in nitrocellulose blotted extract from *Litopenaeus vannamei*. Serum from a Der p 20-sensitized patient was pre-incubated with rDer p 20 (lane 1), with human serum albumin (lane 2) or without inhibitor (lane 3). IgE reactivity was detected with ^{125}I-labelled anti-human IgE and was visualized by autoradiography. The molecular weights in kDa are indicated on the left margins.

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Supplementary References

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