*Allergen Data Collection - Update:*

# Codfish *(Gadus morhua)*

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# Codfish*(Gadus morhua)*

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## Abstract

*IgE-mediated adverse reactions to fish are a problem frequently encountered in fish processing communities. The codfish inhabits the North, Baltic and White Sea, and the Northern Atlantic and Pacific. It is used as a fresh, salted, dried or more recently as a processed food ingredient of e.g. surimi. Although food processing such as cooking and canning could alter the allergenic potency of codfish allergens, one should be aware of the retained significant allergenicity of these products. Fish and its products always should be declared according to a list of the Codex Alimentarius Commission on mandatory labelling of prepackaged foods.*

*Fish allergy is common in food allergic children (> 1 year of age) and young adults. Moreover, fish is considered an important food allergen in adults. Although the exact prevalence is unknown, the frequency of allergy to codfish is estimated to be below 0.5% in the general population and about 5-10% in food allergic individuals from different studies. Reactions, usually immediate type, may occur after ingestion, skin contact, or even after inhaling fish vapour. Skin symptoms, such as urticaria or angio-edema, are observed the most, followed by respiratory and gastrointestinal complaints. In severe cases cardiovasculatory symptoms, including anaphylactic shock, may occur.*
*Codfish amounts as small as a few milligrams can elucidate allergic reactions.*
*SPT and RAST are reliable tools in the diagnosis of codfish allergy.*

*More than 15 different allergens have been identified in codfish. The major allergen Gad c 1 (Allergen M) belongs to the Ca2+-binding parvalbumins and was the first food allergen characterized by its IgE-binding epitope structure . Parvalbumins have been identified as cross-reacting IgE-binding allergens in several fish species such as carp, catfish, dogfish, eel, perch, salmon, snapper, and tuna. Despite the high degree of in-vitro cross-reactivity some species may be tolerated by certain allergic individuals.*
*However, all fish species should be avoided until safe ingestion has been proven by challenge tests.*

*An overview of prevalence data, symptoms, diagnostic and therapeutic features of codfish allergy as well as molecular biological and allergenic properties of codfish allergens is given in tabular form.*
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## Contents

## 1 Prevalence of Codfish Allergy

Prevalence data are based on different diagnostic procedures. While the prevalence of sensitization (sensitivity) can be estimated by SPT, RAST, and immunoblot, a clinical relevant sensitization (allergy) is evaluated by convincing history (anamnesis) or food challenge tests (ideally by DBPCFC).

### 1.1 General Population

Prevalence within the author's selected populations is listed. Those assigned randomly selected ("unselected") with numbers over 500 may be regarded as representative of the "general population". Inclusion criteria may involve circumstances not related to atopic predisposition according to current knowledge.

| Country / Subjects | Allergy / Sensitivity | References |
|---|---|---|
| ***Italy, Florence***<br>children of general population | codfish 0.4-0.5% (calculated by extrapolation) | de Martino et al. 1993 |
| ***Norway, Oslo***<br>general population | codfish 0.1% | Aas 1966 |
| ***Sweden*** *(Göteborg, Uppsala, Västerbotten)*<br>1397 unselected adults, age 20-44 years (study period 1991-92) | fish 0.3% (RAST) | Björnsson et al. 1996 |
| ***UK***<br>16420 randomly selected adults (age >15 years) | fish 0.5% (interview survey, questionnaire) | Emmett et al. 1999 |

### 1.2 Subjects with Atopic or Other Diseases

| Country / Subjects | Allergy / Sensitivity | References |
|---|---|---|
| ***France***<br>81 cases of food- related anaphylaxis (from 1991-92) | fish 10.4% | Moneret-Vautrin & Kanny 1995 |
| ***France***<br>80 cases of food- related anaphylaxis (from 1993-97) | fish 5% | European Commission 1998 |
| ***France, Nancy and Toulouse***<br>544 food allergic children | codfish 6.4% (labial food challenge) | Rance et al. 1999b |
| ***France, Pierre Benite***<br>a) 580 patients with adverse reactions to food<br>b) 60 cases of anaphylaxis (study period 1984-92) | a) fish 24% (RAST)<br>b) fish 13% | Andre et al. 1994 |
| ***France, Toulouse***<br>142 food allergic children | codfish 5.6 % (labial food challenge) | Rance & Dutau 1997 |
| ***France, Toulouse***<br>378 food allergic children | codfish 7.1% (food challenge) | Rance et al. 1999a |
| ***Germany,Bonn***<br>150 children allergic to egg white, milk, codfish, wheat, peanut and/or soybean | codfish 5.3% (RAST) | Liappis & Starke 1999 |
| ***Italy, Bari***<br>134 patients with atopic dermatitis | codfish 5.2 % (case history), 10% (RAST) | Bonifazi et al. 1978 |
| ***Italy, Florence***<br>food allergic children | codfish 18 % (SPT, RAST)<br>of which 66 % had clinical symptoms | Novembre et al. 1988<br>Vierucci et al. 1989 |
| ***Italy, Florence***<br>558 children with atopic diseases | codfish 4.5% (SPT, RAST) | de Martino et al. 1993 |

| | | |
|---|---|---|
| ***Italy, Florence***<br>54 episodes of food-dependent anaphylaxis in 44 children (age 1 month to 16 years) (from 1994-1996) | fish 30% | Novembre et al. 1998 |
| ***Italy, Milan***<br>202 with chronic urticaria and suspected food allergy | fish 0.5% (DBPCFC) | Pigatto & Valsecchi 2000 |
| ***Netherlands***<br>131 cases of food- induced anaphylaxis (from 1993-1997) | fish 3.8%(survey, reported to the TNO Nutrition and Food Research Institute) | European Commission 1998 |
| ***Norway, Oslo***<br>a) food allergic patients<br>b) fish allergic children | a) codfish 4.2%<br>b) codfish 88% | Aas 1966 |
| ***Spain, Madrid***<br>355 food allergic children | fish (cod, tuna) 30% (SPT, RAST) | Crespo et al. 1995 |
| ***Spain, Pamplona***<br>74 patients with atopic dermatitis | fish 22% (SPT, RAST, Histamine Release) | Resano et al. 1998 |
| ***Sweden***<br>55 cases of food- induced anaphylaxis (from 1994-1996) | fish 1.8% (Hospital Reports) | European Commission 1998 |
| ***Switzerland, Zurich***<br>a) 402 food allergic adults (study period 1978-87)<br>b) 383 food allergic patients (study period 1990-94) | a) fish 7.2 %<br>b) fish 9.7%<br>(anamnesis, clinical relevance, diagnostic tests) | a) Wüthrich 1993<br>b) Etesamifar & Wüthrich 1998 |
| ***UK, London***<br>100 patients with food intolerance | fish/shellfish 22% (repeated challenge) | Lessof et al. 1980 |
| ***UK, Manchester***<br>90 patients experienced anaphylactic reactions to foods (from 1994-1996) | fish 2.2% (suspected cause of patients' worst reaction) | Pumphrey & Stanworth 1996 |
| ***USA, Baltimore, MD***<br>20 fish- sensitive patients with atopic dermatitis | fish 55% (DBPCFC) | Sampson & Ho 1997 |
| ***USA, Denver, CO***<br>food allergic children (DBPCFC)<br>a) 74 age of <3 years<br>b) 111 age of 3-19 years | a) fish 4.1%<br>b) fish 4.5%<br>(DBPCFC) | Bock & Atkins 1990 |
| ***USA, Little Rock, AR***<br>165 patients with atopic dermatitis | codfish 6.7% (SPT) of which 3/9 were DBPCFC-positive | Burks et al. 1998 |
| ***USA, Long Beach, CA***<br>137 patients with latex allergy | fish 1.7 % (convincing history of possible IgE mediated symptoms occurring within 60 minutes of ingestion) | Kim & Hussain 1999 |
| ***USA, Portland, ME***<br>39 fish sensitive adults | codfish 31 % (case history), 46 % (SPT), 67 % (RAST)<br>to all tested 17 fish species 26 % (SPT) | Helbling et al. 1996 |

## 1.3 Prevalence of Associated Allergies

| Country / Subjects | Allergy / Sensitivity | | References |
|---|---|---|---|
| ***Italy, Florence***<br>20 children with codfish allergy | eel<br>bass, dentex, sole, and tuna<br>perch and tench<br>anchovy, red mullet, and trout<br>mullet<br>carp<br>gilthead, mackerel, salmon, and sardine<br>dogfish<br>(SPT) | in 85%<br>in 55%, each<br>in 40%, each<br>in 35%<br>in 30%<br>in 25%<br>in 20%, each<br>in 10% | de Martino et al. 1990 |

## 2 Outgrowing / Persistence of Codfish Allergy

| Country / Subjects | Allergy / Sensitivity | References |
|---|---|---|
| ***Finland, Oulu***<br>children with atopic dermatitis | Allergy to fish according to age groups:<br>0-1 year in 5.3%<br>1-3 years in 12%<br>3-15 years in 9.5%<br>(n=57, 43 and 42) (SPT) | Hannuksela 1987 |
| ***France, Nancy and Toulouse***<br>35 children with codfish allergy | Allergy to codfish according to age groups:<br>0-1 year in 0%<br>1-3 years in 29%<br>3-6 years in 31%<br>6-15 years in 40%<br>(SPT and/or RAST, food challenge) | Rance et al. 1999b |

## 3 Symptoms of Codfish Allergy

| Symptoms & Case Reports | References |
|---|---|
| systemic reactions<br>anaphylaxis (6, 7, 9, 10, 14, 12)<br><br>symptoms on skin and mucous membranes<br>angio-edema (2, 3, 8, 11, 15), conjunctivitis (16), eczema (2), itchy eyes (14), genralized pruritus (16), urticaria (2, 3, 8, 11, 13, 15, 16), contact urticaria (4, 5), generalized urticaria (5, 14)<br><br>gastrointestinal symptoms<br>emesis (16), itching in throat (14), nausea (16), oral allergy (16), oropharyngeal itching and swelling (7), vomiting (3)<br><br>respiratory symptoms<br>allergic rhinitis (15), asthma (1, 2, 8, 13), cough (14), cyanosis (11), dyspnoea (14, 16), wheeze (11, 14)<br><br>other symptoms<br>headache (16) | (1) DeBesche 1937<br>(2) Aas 1978<br>(3) Bonifazi et al. 1978<br>(4) Beck & Knudsen-Nissen 1983<br>(5) Ferre et al. 1985<br>(6) Yunginger et al. 1991<br>(7) Hansen & Bindslev-Jensen 1992<br>(8) de Martino et al. 1993<br>(9) Andre et al. 1994<br>(10) Moneret-Vautrin & Kanny 1995<br>(11) Casimir et al. 1997<br>(12) James et al. 1997<br>(13) Bugajska-Schretter et al. 1998<br>(14) Lin et al. 1998<br>(15) Patriarca et al. 1998<br>(16) Helbling et al. 1999 |

***Percentage of Reactions***

| Symptoms / Ref. | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| Anaphylaxis / Shock | | | 8% | | 6% |
| Fainting | | | 5% | | |
| Cutaneous | | | | 91% | |
| Angioedema | | | 51% | | |
| Atopic dermatitis | | | | | 23% |
| Pruritus | | | 69% | | |
| Urticaria | | | 69% | | |
| Urticaria / Angioedema | 18% | 34% | | | 49% |
| Gastrointestinal | | | | 64% | |
| Dyspepsia / cramps | | | 18% | | |
| Oral allergy syndrome | | | | | 3% |
| Vomiting | | | 8% | | |
| Respiratory | | | | 9% | |
| Asthma / wheezing | | 60% | 54% | | 20% |
| No. of patients | 22 | 68 | 39 | 11 | 35 |

(1) fish allergic patients, other symptoms: 73 % asthma / eczema, 9% abdominal symptoms or rhinorrhoea only
(2) codfish allergic children
(3) fish sensitive adults
(4) fish allergic patients with atopic dermatitis
(5) codfish allergic children

(1) Lessof et al. 1980
(2) de Martino et al. 1993
(3) Helbling et al. 1996
(4) Sampson & Ho 1997
(5) Rance et al. 1999b

***Threshold for Elicitation of Symptoms***

Amounts of codfish inducing symptoms ranged from 6 mg to 6.7 g (anaphylactic reactions 25-50 g) (DBPCFC, 10 codfish allergic adults) (1)

Subjective symptoms at doses of 1 g codfish in 71% and at subsequent doses of 4 g in 29% of patients; objective symptoms at doses of 1 g in 14%, at doses of 4 g in 29%, and at doses of 64 g in 14% of patients (DBPCFC, 7 codfish allergic adults) (2)

Amounts of dehydrated fish smaller than 500 mg induced symptoms in 17% of patients (DBPCFC, 12 fish allergic children with atopic dermatitis) (3)

(1) Hansen & Bindslev-Jensen 1992
(2) Helbling et al. 1999
(3) Sicherer et al. 2000

## 4 Diagnostic Features of Codfish Allergy

| Parameters / Subjects | Outcome | References |
|---|---|---|
| ***Onset of Symptoms, Male:Female Ratio, IgE-level***<br>a) 68 codfish allergic children<br>b) 533 children allergic to other inhalant and/or food allergens | Onset of asthma significantly lower in codfish allergic children (P <0.001):<br>a) 32 months, b) 41 months<br>Significant higher male:femal ratio in codfish allergic children:<br>a) 3.53, b) 1.78 and 0.68 in children allergic to inhalants and foods<br>Significant higher specific serum IgE in codfish allergic children (P <0.001, RAST):<br>a) 14.27 +/- 3.87 kU/L<br>b) 8.12 +/- 4.06 kU/L | de Martino et al. 1993 |
| ***SPT and IgE***<br>codfish allergic adults | Significant correlation between SPT and RAST (P<0.0005) | Helbling et al. 1996 |

| | | |
|---|---|---|
| ***SPT, IgE and Clinical Relevance***<br>20 codfish allergic patients | SPT and RAST were found to be reliable for the diagnosis of allergy to codfish | Aas 1978 |
| ***SPT, IgE, Histamine Release and DBPCFC***<br>10 codfish allergic adults | For identification of DBPCFC-positive subjects, skin prick test and RAST proved to be the most sensitive tests (7/7) (specificity of all tests 90-97 %) | Hansen & Bindslev-Jensen 1992 |
| **a)** ***RAST and DBPCFC***<br>**b)** ***Histamine Release (HR) and DBPCFC***<br>8 codfish allergic adult | a) RAST with commercial extracts and fresh food:<br>sensitivity 100%<br>specificity 87-100%<br>b) HR with commercial extracts and fresh food:<br>sensitivity 83%<br>specificity 100% | Hansen et al. 1996 |
| **a)** ***RAST and DBPCFC***<br>**b)** ***SPT and DBPCFC***<br>food-allergic children with atopic dermatitis | a) predictive values of fish specific IgE > 0.35 kU/L<br>positive predictive value 49%<br>(95% for IgE > 20 kU/L)<br>negative predictive value 97%<br>b) predictive values of SPT ( > 3 mm)<br>positive predictive value 77%<br>negative predictive value 80% | Sampson & Ho 1997 |
| ***RAST, SPT and DBPCFC***<br>a) 7 codfish sensitized adults (SPT, history)<br>b) 9 fish allergic adults (tested fish species: catfish, codfish, and snapper) | a) RAST positivity in 71%<br>b) Correlation to DBPCFC: RAST SPT<br>positive predictive value 73% 74%<br>negative predictive value 33% 100% | Helbling et al. 1999 |

## 5 Therapy of Codfish Allergy

| Treatment* | Outcome | References |
|---|---|---|
| ***Elimination Diet***<br>7 children (8-48 months of age) sensitized to fish (RAST, SPT), all children tolerated fish at the beginning of elimination diet | Instituting fish-free diet based on positive skin test to fish and associated atopic dermatitis in 5 (plus asthma in one). Effects of elimination diet after 1-96 months (mean 36 months):<br>Improvement of atopic dermatitis in 2 patients.<br>Accidental exposure to fish inducing severe symptoms during elimination diet after 24-111 months (mean 70 months): after ingestion in 3 patients (7 occasions), after inhalation in 4 patients (7 occasions), and after skin contact in 4 patients (7 occasions). SPT and RAST remained unchanged or increased after elimination diet. | Larramendi et al. 1992 |
| ***Immunotherapy***<br>1 fish/codfish allergic child | Uncooked codfish odors and accidentally eaten pieces of codfish were tolerated after therapy (immunotherapy administered by daily subcutaneous injections following the schedule for insect venom allergy using codfish extracts) | Casimir et al. 1997 |
| ***Oral Desentization***<br>a) 2 codfish allergic patients<br>b) 7 fish allergic patients | A diluted food extract followed by increased pure boiled codfish was administered following a standardized protocol, after therapy codfish was tolerated (maintenance dose: 200 g boiled fish / week)<br>a) treatment successfully completed, length of therapy 3 and 5 months<br>b) treatment successfully completed in 5 cases in 4-10 months | a) Patriarca et al. 1998<br>b) Nucera et al. 2000 |

* Studies may be experimental, unproved, or controversial. Please notice the disclaimer !

## 6 Composition of Codfish

### 6.1 Distribution of Nutrients

For other celery products see: USDA Nutrient Database

| **Nutrients:** Content per 100 g | | |
|---|---|---|
| Energy 316 kJ (74 kcal) | **Vitamins** | Phe 840 mg |
| Water 80.8 g | Vitamin A 10 µg | Thr 970 mg |
| Protein 17.7 g | Vitamin D 1 µg | Trp 240 mg |
| Lipids 0.4 g | Vitamin E 260 µg | Tyr 710 mg |
| Minerals 1.1 g | Vitamin B1 55 µg | Val 1090 mg |
| | Vitamin B2 50 µg | |
| **Minerals** | Nicotinamide 2300 µg | **Lipids** |
| Sodium 70 mg | Pantothenic acid 120 µg | Palmitic acid 55 mg |
| Potassium 355 mg | Vitamin B6 200 µg | Stearic acid 13 mg |
| Magnesium 25 mg | Biotin 1-3 µg | Oleic acid 50 mg |
| Calcium 25 mg | Folic acid 12 µg | Linolic acid 4 mg |
| Manganese 17 µg | Vitamin B12 1 µg | Linoleic acid 2 mg |
| Iron 440 µg | | Arachidonic acid 3 mg |
| Copper 230 µg | **Amino Acids** | Eicosapentaenoic acid 35 mg |
| Zinc 500 µg | Arg 1210 mg | Docosahexaenoic acid 55 mg |
| Phosphorus 185 mg | His 520 mg | Cholesterol 45 mg |
| Chloride 230 mg | Ile 990 mg | |
| Fluoride 30 µg | Leu 1690 mg | **Other** |
| Iodine 120 µg | Lys 2050 mg | Purines 110 mg |
| Selenium 30 µg | Met 600 mg | |

Reference: Deutsche Forschungsanstalt für Lebensmittelchemie, Garching bei München (ed), **Der kleine "Souci-Fachmann-Kraut" Lebensmitteltabelle für die Praxis**, WVG, Stuttgart 1991

### 4.2 Proteinfraction

| **Proteins / Glycoproteins** | **Amount** of total protein |
|---|---|
| 41-kDa Allergen | 18 µg / 100 µg crude protein extract |

Reference: Galland et al. 1998

## 7 Allergens of Codfish

| Proteins / Glycoproteins | Allergen Nomenclature | References |
|---|---|---|
| Allergen M [12-13 kDa] | Gad c 1* | Elsayed & Bennich 1975 |
| 41-kDa Allergen | | Galland et al. 1998 |
| Allergen: 63 kDa | | Mata et al. 1994 |
| Allergens: 12, 21, 24, 33, 47, 61 kDa | | Hemmens et al. 1989 |
| Allergens: 12, 18, 22, 23, 26, 31, 33, 35, 37, 43, 49, 56, 69, 81, > 97 kDa | | Hansen et al. 1996 |
| Allergens: 12, 15, 20, 25, 30, 35, 66, 80, 100, 200 kDa | | Bugajska-Schretter et al. 1998 |
| Allergens: 12, 18, 41, 60, 67, 80, 104, 130 kDa | | Dory et al. 1998 |
| Allergens: 13, 22, 28, 41, 49, 60 kDa | | Galland et al. 1998 |

* according to latin name of the baltic cod *(Gadus morhua callarias)*

### 7.1 Sensitization to Codfish Allergens

| Country / Subjects | Sensitivity to | References |
|---|---|---|
| ***Austria, Vienna***<br>28 codfish allergic patients | 12 kDa allergen (Gad c 1) in 100 %<br>(SDS-PAGE immunoblot) | Bugajska-Schretter et al. 1998 |
| ***Denmark, Copenhagen***<br>8 codfish allergic adults | 12-13 kDa allergen in 100 % of DBPCFC- positive patients (SDS-PAGE immunoblot) | Hansen et al. 1996 |
| ***France, Nantes***<br>12 codfish allergic patients | 12 kDa allergen: relative IgE- binding 50%<br>30 and 67 kDa allergens: about 10%<br>of total IgE binding to crude extract (pooled serum, SDS-PAGE immunoblot) | Dory et al. 1998 |
| ***Norway, Bergen*** (a)<br>***Australia, St. Leonards*** (b)<br>a) 2 codfish , b) 1 fish allergic patient | 6 allergens recognized by all patients' sera, relative intensity of IgE- binding: 12 kDa >> 21, 24 kDa > 33, 47, 61 kDa (SDS-PAGE immunoblot) | Hemmens et al. 1989 |
| ***Norway, Bergen***<br>a) 11 codfish allergic patients<br>b) fish allergic patients | 12 kDa allergen (Gad c 1)<br>(a) ELISA inhibition<br>(b) SDS-PAGE immunoblot | a) Lindstrøm et al. 1996<br>b) van Do et al. 1999 |
| ***Norway, Oslo***<br>codfish allergic patients | At least 7 IgE- binding precipitates (CRIE) | Aukrust et al. 1978 |

## 7.2 Properties of Allergen M (Gad c 1)

### 7.2.1 Molecular Biological Properties

| Allergen M | References |
|---|---|
| ***Allergen Nomenclature*** Gad c 1 | (1) Larsen & Lowenstein 1999 |
| ***Molecular Mass***<br>12.328 kDa (calculated) (1)<br>12-13 kDa (SDS-PAGE) (2) | (1) Elsayed & Bennich 1975<br>(2) Hansen et al. 1996 |
| ***Isoelectric Point*** pI 4.75 (1) | (1) Elsayed & Aas 1971 |
| ***Amino Acid Sequence,mRNA, and cDNA***<br>**Gad c 1**<br>**SWISS-PROT:** P02622<br>**PIR:** PVCD<br>**Amino Acids** 113 (1)<br>**mRNA**<br>**cDNA** | (1) Elsayed & Bennich 1975 |
| ***Genetic Variants / Isoforms***<br>2 IgE-binding precipitates in CRIE (1) | (1) Aukrust et al. 1978 |
| ***Posttranslational Modification***<br>Acetylation:<br>N-terminal acetylation (1)<br><br>Glycosylation:<br>1 mol Glucose per mol Gad c 1 (2)<br>Glycosylation site: aa Cys-18 (2) | (1) SWISS-PROT<br>(2) Elsayed & Bennich 1975 |
| ***Biological Function***<br>EF-hand calcium binding protein arranged in 3 domains (AB, CD, and EF); domains CD and EF bind 1 Ca2+ ion each; belongs to parvalbumin subfamily, propably involved in muscle relaxation (1, 4)<br>2 Ca++-binding sites:<br>site 1: aa 51 and aa 62 (5) on loop aa 49-64 (2)<br>site 2: aa 90 and 101 (5) on loop aa 88-103 (3) | (1) SWISS-PROT<br>(2) Elsayed et al. 1980<br>(3) Elsayed et al. 1981<br>(4) Elsayed & Apold 1983<br>(5) Permyakov et al. 1987 |
| ***Sequence Homology***<br>Whole sequence from Allergen M to other paralbumins:<br>From carp and hake aa 68 and 65 % identity (1)<br>From frog, turtle, chicken, and rat aa 50-60 % identity (1)<br>From salmon parvalbumin cDNA clone 24.1 and clone 14.1: aa 58% and 51% identity (2)<br>Sequence aa 90-102 from Allergen M to IgE- binding epitope 1 from Sj22.6 (allergen from *Schistosoma japonicum)*: (aa 54 % identity,) aa 85 % homology (3) | (1) PIR-BLAST<br>(2) Lindstrøm et al. 1996<br>(3) Santiago et al. 1998 |

## 7.2.2 Allergenic Properties

| Allergen M | References |
|---|---|
| ***Frequency of Sensitization***<br>IgE-binding to Allergen M in 100 % (1) | (1) see 5.1 Sensitization to Codfish Allergens |
| ***B-Cell Epitopes***<br>IgE-binding regions of Allergen M (5):<br><br>aa 13-32 (synthetic peptide) (6)<br>aa 33-44 (trypsin digest) (1)<br>aa 49-64 (synthetic peptide) (3)<br>aa 88-103 (synthetic peptide) (4)<br>aa 88-108 (trypsin digest), 62 % (a) (2)<br>aa 88-113 (trypsin digest), 87 % (a) (2)<br>aa 97-113 (trypsin digest), 15 % (a) (2)<br><br>(a) RAST inhibition of IgE- binding to Allergen M<br><br>Amino acids critical for IgE-binding<br>on region aa 49-64: two repetitive sequences (DEDK) and (DELK) spaced by 6 unrelated residues (7) | (1) Elsayed et al. 1976<br>(2) Elsayed & Apold 1977<br>(3) Elsayed et al. 1980<br>(4) Elsayed et al. 1981<br>(5) Elsayed & Apold 1983<br>(6) Elsayed et al. 1983<br>(7) Elsayed et al. 1991 |
| ***Alteration of Allergenicity***<br>amino acid modification:<br>acetylation of Tyr-30 decreased allergenic activity, modification of Arg-75 did not (1, 3)<br><br>Ca2+ binding:<br>Unchelating of Ca2+ with EDTA or masking of Arg-75 by cyclohexanedione condensation decreased allergenicity about 25 % (2, 3)<br>Reduction of IgE- binding to Allergen M after Ca2+- depletion (SDS-PAGE immunoblot) (4)<br><br>Oxidation / Deglycosylation:<br>Significant reduction of IgE- binding to Allergen M after periodate treatment (SDS-PAGE immunoblot) (4)<br><br>Polymerization:<br>Polymerization of Allergen M deminished allergenicity (1, 2, 3)<br>Polymerization of fragment TM 1 (aa 1-75) reduced allergenicity, while polymerization of fragment TM 2 (aa 76-113) to trimer increased its allergenic reactivity (1, 2, 3)<br><br>Reduction:<br>No change in IgE-binding after reduction with 2-mercaptoethanol (SDS-PAGE immunoblot) (4) | (1) Apold & Elsayed 1979<br>(2) Apold & Elsayed 1980<br>(3) Elsayed & Apold 1983<br>(4) Bugajska-Schretter et al. 1998 |

## 7.3 Properties of 41-kDa Allergen

### 7.3.1 Molecular Biological Properties

| 41-kDa Allergen | References |
|---|---|
| ***Allergen Nomenclature*** none | |
| ***Molecular Mass***<br>41 kDa (SDS-PAGE) (1) | (1) Galland et al. 1998 |
| ***Isoelectric Point*** pI 5.8 (1) | (1) Galland et al. 1998 |
| ***Amino Acid Composition***<br>Amino acid composition (1)<br>N-terminal aa: Asp (1) | (1) Galland et al. 1998 |
| ***Biological Function***<br>Calcium binding protein as determined by anti-parvalbumin mAb (specific for calcium bound form of parvalbumin) (1) | (1) Galland et al. 1998 |

### 5.3.2 Allergenic Properties

| 41-kDa Allergen | References |
|---|---|
| ***Frequency of Sensitization***<br>IgE-binding to 41-kDa Allergen by pooled serum from cod allergic patients (1) | (1) Galland et al. 1998 |

## 8 Isolation & Preparation

| Extract / Purified Allergens | Methods | References |
|---|---|---|
| Protein extract | Extraction of raw and cooked fish with PBS-buffer overnight at 4°C, centrifugation, lyophilization | Bernhisel-Broadbent et al. 1992 |
| Muscle and Surimi extract | Extraction of raw codfish and surimi with 2 % sodium chloride solution for 18 h, centrifugation, purification by gelfiltration (Sephacryl S200) | Mata et al. 1994 |
| Muscle extract | Homogenization of raw muscle under liquid nitrogen, dissolved in electrophoresis sample buffer | Bugajska-Schretter et al. 1998 |
| Muscle extract | Fillets of pre- rigor mortis and post- rigor mortis codfish were cut and placed into liquid nitrogen, crushed and homogenized in phosphate- buffer (for sarcoplasmic proteins) or PBS-buffer (for myofibrillar proteins) at 4°C, centrifuged and lyphilized | Dory et al. 1998 |
| Allergen M | Purification of myogen fraction by ion-exchange chromatography (DEAE) and gelfiltration (Sephadex G-75) | Aas & Jepsen 1967<br>Aas & Elsayed 1969 |
| Allergen M | Purification of myogen fraction by isoelectric fractionation | Elsayed & Aas 1971 |
| 41-kDa Allergen | Isolation from a crude cod extract by ammonium sulfate fractionation, hydroxyapatite chromatography and preparative electrophoresis | Galland et al. 1998 |

## 9 Cross-Reactivities

| Cross-Reacting Allergens | Subjects / Methods | References |
|---|---|---|
| ***Codfish*** bass, dentex, eel, sole, and tuna (17 different fish species tested) | Cross-reacting allergens in cod, bass, dentex, eel, sole, and tuna, inhibition range from 73 - 96 % (RAST inhibition) | de Martino et al. 1990 |
| ***Codfish*** 10 different fish species (bass, catfish, flounder, mackerel, perch, salmon, trout, tuna, sardine) | 11 fish allergic patients: 7 patients sensitive to only 1 species, 1 patient to 2 species, and 2 patients to 3 species (oral challenge)<br>8 patients sensitive to all 10 species in SPT<br>Cross-reactivity did not necessarily correlate with clinical relevance (RAST inhibition) | Bernhisel-Broadbent et al. 1992 |
| ***Codfish*** salmon | Inhibition of IgE-binding to salmon by codfish (ELISA inhibition) | Lindstrøm et al. 1996 |
| ***Codfish*** mackerel, herring, and plaice | Inhibition of IgE- binding to codfish extract by mackerel, herring, and plaice in 8 codfish allergic patients, no cross-reactivity to shrimp or milk (RAST inhibition) | Hansen et al. 1997 |
| ***Codfish*** catfish, dogfish, snapper (12.5 kDa allergens) | Inhibition of IgE- binding to 12.5 kDa allergens by codfish extract (immunoblot inhibition) | James et al. 1997 |
| ***Codfish*** tuna, salmon, perch, carp, and eel | Inhibition of IgE- binding to extracts from tuna, salmon, perch, carp, and eel by codfish ranged from 43 - 97 % in 4 fish allergic patients (RAST inhibition) | Bugajska-Schretter et al. 1998 |
| ***Codfish*** tuna, salmon, perch, carp, and eel (12 kDa) | Inhibition of IgE- binding to 12 kDa parvalbumins from different species by codfish extract (immunoblot inhibition) | Bugajska-Schretter et al. 1998 |
| ***Codfish Allergens*** (12 kDa) 17, 21, 24, and 47 kDa- codfish allergens * | Gad c 1 (12 kDa) bound IgE was eluted and rebound to 12, 17, 21, 24, and 47 kDa allergens in 1 patient, while in another patient IgE rebound only to 12 kDa allergen (SDS-PAGE immunoblot) | Hemmens et al. 1989 |
| ***Codfish Allergens*** 12, 22, 25, 30, 45, 50, 60, 67, 80, 104, and 130 kDa- codfish allergens * | Exept for the 41, 49, and 55 kDa allergens all IgE-binding proteins from codfish were detected by antiparvalbumin specific antibody (SDS-PAGE immunoblot) | Dory et al. 1998 |
| ***Codfish*** (12 kDa) salmon (Sal s 1) * | Gad c 1 (12 kDa) and Sal s 1 have some homologous allergenic epitopes (SDS-PAGE immunoblot) | van Do et al. 1999 |

* multiple sensitization / reactivity (not proved by inhibition-tests)

## 10 Stability of Codfish Allergens

| Treatment | Effects | References |
|---|---|---|
| ***Cod myogen fraction*** *(Enzymic Hydrolysis)* enzymic digestion for a) 48 h, b) < 24 h and c) < 2 h at 37°C (stopped by heating to 80°C, 10 min) | a) Loss of allergenic activity by treatment with trypsin, pepsin, subtilisin or pronase, appr. 50% decrease in allergenic activity by elastase<br>b) Remaining allergenic activity by pronase treatment<br>c) Remaining allergenic activity by trypsin or pepsin treatment | Aas & Elsayed 1969 |
| ***Codfish Allergens*** *(Detergents)* 9 household cleaning solutions and 5 chemical detergents mixed with codfish allergen extract, incubation for 20 min at RT | Guanidine hydrochloride and sodium lauryl sulphate induced some modifications of allergen patterns;<br>None of the detergents totally destroyed the allergenic activities, even when used in concentrations up to 10 times than recommended<br>(CIE, CRIE, serum pool of >5 patients) | Dybendal et al. 1990 |
| ***Codfish Allergens*** *(Heat)* raw and cooked codfish | Number of protein bands in raw and cooked codfish: 25 and 23, respectively (SDS-PAGE)<br>Lower intensity of IgE- binding to allergens from cooked codfish (SDS-PAGE immunoblot) | Bernhisel-Broadbent et al. 1992 |
| ***Codfish Allergens*** *(Heat)* raw and boiled (6 min, 1 h, 4 h) codfish, mackerel, herring, and plaice | Except for mackerel all allergens seemed stable in histamine release test, bands >40 kDa were more heat sensitive, allergens detected in all extracts even after 4 h of boiling and in boiling water (2 codfish allergic patients, SDS-PAGE immunoblot) | Hansen et al. 1994 |
| ***Pizza Toppings*** *(Heat)* uncooked and cooked pizza toppings | IgE-binding to uncooked pizza topping extract was inhibited by cooked pizza toppings (max. 76%), pollack (max. 59%), cod (max. 30%), and surimi (max. 52%) (30 fish sensitive patients, RAST inhibition) | Helbling et al. 1992 |
| ***Codfish Allergens*** *(Storage)* a) pre- and post-rigor mortis<br>b) stored commercial codfish (several days) | a) No difference in IgE- binding patterns<br>b) Storage might increase relative IgE- binding, additional bands 18, 41, and 80 kDa allergens (RAST inhibition, SDS-PAGE immunoblot) | Dory et al. 1998 |

## 11 Allergen Sources

| Reported Adverse Reactions | References |
|---|---|
| ***Food / Food additives*** Fatal anaphylactic reaction in fish allergic patient after ingestion of potatoes fried in same oil that has been used for fish (1)<br>Anaphylactic reactions in fish allergic boy after ingestion of different kinds of fish (cod, tuna, salmon, trout, eel...), fish soup, chopsticks contaminated with fish preparations or canned fish (2) | (1) Yunginger et al. 1988<br>(2) Lin et al. 1998 |

| Allergens in Codfish Products | Results | References |
|---|---|---|
| ***Codfish Allergens*** 63 kDa allergen in surimi, a Japanese food product containing fish meat that also may contain starch, egg white, and other ingredients | Surimi extract gave positive reactions in 6 codfish allergic patients (RAST, RAST inhibition, Histamine Release, SDS-PAGE) | (1) Mata et al. 1994 |
| ***Fish Allergens*** Fish allergens in surimi and pizza toppings | Extracts of surimi, uncooked and cooked pizza toppings gave positive reactions in fish sensitive patients (RAST, RAST inhibition) | (1) Helbling et al. 1992 |

| | | |
|---|---|---|
| ***Anisakis simplex***<br>Anisakis simplex, a parasite of fish and cephalopods | Specific IgE to A. simplex (> 0.7 kU/l) in 22 patients with urticaria/angio-edema after fish ingestion, of which 8 were diagnosed as having A. simplex allergy (RAST, clinical symptoms) | (1) Del Pozo et al. 1997 |

| Other Allergen Sources | References |
|---|---|
| ***Dust***<br>Dust samples from fitted-carpets and linoleum floors in schools in Norway contained codfish allergens, higher contents in samples from carpets | Dybendal et al. 1989a, 1989b |
| ***Air Samples: Fish Market***<br>Passively aerosolized fish allergens in samples from an open-air fish market: detectable fish allergen content (2-25 ng/m$^3$ ) on 39 of 41 days (air sampling, IgE-ELISA) | Taylor et al. 2000 |

## 12 Food Allergen Labelling

| Food Allergen | Labelling / Regulation Status | References |
|---|---|---|
| ***International Regulations***<br>Fish and fish products | mandatory labelling of prepackaged food / advisary status (1) | (1) Codex Alimentarius Commission 1999 |
| ***European Regulations***<br>Fish and fish products | labelling appropriate / recommendation (1) | (1) Bousquet et al. 1998 |

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## Common Abbreveations

| | |
|---|---|
| 2D | two-dimensional |
| 3D | three-dimensional |
| aa | amino acid(s) |
| Ab | antibody |
| Act c 1, 2 | nomenclature of kiwi fruit allergens *(Actinidia chinensis)* |
| Api g 1-5 | nomenclature of celery allergens *(Apium graveolens)* |
| Ara h 1-7 | nomenclature of peanut allergens *(Arachis hypogaea)* |
| Bos d 4, 5, 6, 7, 8 | nomenclature of cow's milk allergens *(Bos domesticus)* |
| C | concentration of N,N'-methylenbisacrylamide (crosslinker) |
| Cas s 1, 5 | nomenclature of chestnut allergens *(Castanea sativa)* |
| CAST | cellular antigen stimulation test |
| CCD | cross-reactive carbohydrate determinants |
| CICBAA | Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire (France) |
| CIE | crossed immunoelectrophoresis |
| CNBr | cyanogen bromide |
| cIEF | capillary isoelectric focussing |
| CLA | cutaneous lymphocyte antigen |
| CLIE | crossed line immunoelectrophoresis |
| CMA | cow's milk allergy |
| CRIE | crossed radioimmunoelectrophoresis |
| Cor a 1 | nomenclature of hazel pollen allergens *(Corylus avellana)* |
| Cyn d 1 | nomenclature of bermuda grass pollen allergens *(Cynodus dactylus)* |
| DBPCFC | double-blind, placebo-controlled food challenge |
| DEAE | diethylaminoethyl (cellulose) (anion exchanger) |
| DNA | deoxyribonucleic acid |
| EAST | enzyme allergosorbent test |
| EC | enzyme classification system |
| EDTA | ethylenediaminetetraacetic acid, disodium salt |
| ELISA | enzyme linked immunosorbent assay |
| EW | egg white |
| Fuc | fucose |
| Gad c 1 | nomenclature of baltic cod allergen *(Gadus callarias)* |
| Gal | galactose |
| Gal d 1-5 | nomenclature of egg allergens *(Gallus domesticus)* |
| GlcN | glucosamine |
| GlcNAc | N-acetylglucosamine |
| Gly m 1, 2, 3 | nomenclature of soybean allergens *(Glycine max)* |
| Hev b 1-10 | nomenclature of latex allergens *(Hevea brasiliensis)* |
| HLA | human leucocyte antigen |
| Hol l 1 | nomenclature of sweet velvet grass allergens *(Holcus lanatus)* |
| HPLC | high performance liquid chromatography |
| HR | Histamine Release |
| IEC | ion exchange chromatography |

| | |
|---|---|
| IEF | isoelectric focussing |
| Ig | immunoglobulin |
| IL | interleukin |
| INF-gamma | interferon-gamma |
| Lol p 1 | nomenclature of rye grass allergens *(Lolium perenne)* |
| LTA4 | leukotriene A4 |
| LTB4 | leukotriene B4 |
| LTC4 | leukotriene C4 |
| LY | lysozyme |
| Man | mannose |
| Mal d 1, 2, 3 | nomenclature of apple fruit allergens *(Malus domestica)* |
| MALDI-MS | matrix-assisted laser-induced desorption/ionization mass spectrometry |
| MAST | multiple allergen sorbent test |
| MHC | major histocompatibility complex |
| Mr | molecular mass |
| Mus a 1 | nomenclature of banana allergens *(Musa* spp.*)* |
| NeuNAc | N-acetylneuraminic acid |
| NMR | nuclear magnetic resonance (spectroscopy) |
| NPV | negative predictive value |
| NRL | natural rubber latex |
| OA | ovalbumin |
| OAS | oral allergy syndrome |
| OM | ovomucoid |
| Ory s 1 | nomenclature of rice allergens *(Oryza sativa)* |
| OT | ovotransferrin |
| PAGE | polyacrylamide gel electrophoresis |
| PBMC | peripheral blood mononuclear cells |
| PBS | phosphate buffered saline |
| Phl p 1 | nomenclature of timothy grass allergens *(Phleum pratense)* |
| pI | isoelectric point |
| PCA | passive cutaneous anaphylaxis (test) |
| PCR | polymerase chain reaction |
| PPT | prick to prick test (skin test with fresh foods) |
| PPV | positive predictive value |
| Prs a 1 (Pers a 1) | nomenclature of avocado allergens *(Persea americana)* |
| Pru av 1, 2, 4 | nomenclature of sweet cherry allergens *(Prunus avium)* |
| Pru p 3 | nomenclature of peach allergens *(Prunus persica)* |
| PVDF | polyvinyliden difluoride |
| PVPP | polyvinyl polypyrrolidone |
| RAST | radioallergosorbent test |
| RBL cells | rat basophil leukaemia cells |
| RIEP | radioimmunoelectrophoresis |
| RNA | ribonucleic acid |
| RT | room temperature |
| SAFT | skin application food test |

| | |
|---|---|
| SDS | sodium dodecylsulfate |
| SEC | size exclusion chromatography |
| SPT | skin prick test |
| T | total acrylamide concentration |
| TCC | T-cell clone |
| TCL | T-cell line |
| TGF-beta-1 | transforming growth factor beta-1 |
| TH | thermolysin |
| TNF-alpha | tumor necrosis factor alpha |
| TR | trypsin |
| Tris | tris-(hydroxymethyl)aminomethane |
| WgA | wheat germ agglutinin |
| Xyl | xylose |

## Abbreveations of DNA-encoded Amino Acids

| | | | | | |
|---|---|---|---|---|---|
| Alanine | Ala | A | Leucine | Leu | L |
| Arginine | Arg | R | Lysine | Lys | K |
| Asparagine | Asn | N | Methionine | Met | M |
| Aspartic acid | Asp | D | Phenylalanine | Phe | F |
| Cysteine | Cys | C | Proline | Pro | P |
| Glutamine | Gln | Q | Serine | Ser | S |
| Glutamic acid | Glu | E | Threonine | Thr | T |
| Glycine | Gly | G | Tryptophan | Trp | W |
| Histidine | His | H | Tyrosine | Tyr | Y |
| Isoleucine | Ile | I | Valine | Val | V |