IMMUNOCAP® MOLECULAR ALLERGOLOGY
REVOLUTIONISING THE WAY YOU LOOK AT ALLERGY
Over View – An Introduction to Molecular Allergology

- What are allergen components?
- What types of diagnostics are there?
  - ImmunoCAP Components
  - ImmunoCAP ISAC
- Back ground – allergen component
- Studies
Molecular diagnosis in allergy

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Summary
Development and progress made in the field of recombinant allergens have allowed for the development of a new concept in allergy diagnosis, molecular diagnosis (MD), which makes it possible to identify potential disease-eliciting molecules. Microarray-based testing performed with a small amount of serum sample enables clinicians to determine specific IgE antibodies against multiple recombinants or purified natural allergen components. Performance characteristics of allergens so far tested are comparable with current diagnostic tests, but have to be confirmed in larger studies. The use of allergen components and the successful interpretation of test results in the clinic require some degree of knowledge about the basis of allergen components and their clinical implications. Allergen components can be classified by protein families based on their function and structure. This review provides a brief overview of basic information on allergen components, recombinants or purified, currently available or soon to become commercially available in ImmunoCAP or ISAC® systems, including names, protein family and function. Special consideration is given to primary or species-specific sensitization and possible cross-reactivity, because one of the most important clinical utility of MD is its ability to reveal whether the sensitization is genuine in nature (primary, species-specific) or if it is due to cross-reactivity to proteins with similar protein structures, which may help to evaluate the risk of reaction on exposure to different allergen sources. MD can be a support tool for choosing the right treatment for the right patient with the right timing. Such information will eventually give clinicians the possibility to individualize the actions taken, including an advice on targeted allergen exposure reduction, selection of suitable allergens for specific immunotherapy, or the need to perform food challenges. Nevertheless, all in vitro tests should be evaluated together with the clinical history, because allergen sensitization does not necessarily imply clinical responsiveness.

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Allergy Diagnosis – Historical Overview

**In-vivo** testing

- 1880: *In-vivo* testing
- 1967: Provocation testing
- 1988-91: Characterisation of IgE
- 1995-1999: First allergens cloned
- 2000: Recombinant allergen panels. 1st CRD.
- 2007: ImmunoCAP ISAC ® goes global

**In-vitro** testing

- 1880: *In-vitro* testing
- 1967: ImmunoCAP ®
- 1988-91: RAST
- 1995-1999: First allergen chip
- 2000: Component-resolved diagnosis

First allergens cloned
Recombinant allergen panels. 1st CRD.
First allergen chip
ImmunoCAP ISAC ® goes global

**Provocation testing**

**Characterisation of IgE**

**ImmunoCAP ®**

**RAST**
How can Molecular Allergology improve clinical practice?

• What is triggering the reaction?
• Is this true allergy or is the patient sensitised?
• Is the patient at risk to severe allergy?
• How can I rationalise oral food challenges?
• Can I make immunotherapy more effective in this patient?

Allergen components are the foundation of accurate allergy diagnosis and appropriate follow-up.
Limitations of Current – Allergy Testing

• Current tests define allergen-containing sources (whole allergen), not specific allergenic molecules
• Up to 50% of patients have asymptomatic sensitisation¹
• Up to 30% patients with false positive results in “open” challenges due to bias²

• The major challenge to clinicians is distinguishing sensitisation versus true allergy³

Cross Reactivity? What is it?

Pollen

IgE to Grass Pollen

Sensitisation

IgE to Grass Pollen

Grass Profilin, Phl p 12
(Primary Sensitiser)

Allergen protein molecule families are very similar in their macro molecular structure.

Peanut Profilin, Ara h 5*
(Possible Cross Reactivity)
Two platforms

ImmunoCAP Allergen Components
• Specific IgE
  • Over 85 different specific IgE component diagnostics

ImmunoCAP ISAC
• Used for unidentified allergy – ‘patient profile’
  • 21st Century allergy diagnostics
  • Protein array biochip
  • 103 individual components
What is an allergen protein?
More than one Protein

Proteins of Peanut

Ara h 1

Ara h 2

Ara h 3

Ara h 8

Ara h 9
NATIVE ALLERGEN EXTRACT → NATIVE/RECOMBINANT PROTEINS A, B, AND C

A mixture of allergens and non-allergenic substances

Component A

Component B

Component C
Component Nomenclature

Ara h 2

*Arachis hypogaea*, allergen # 2

Prefix "r" for recombinant or "n" for native

rAra h 2
Protein groups

Plant Foods

**PR-10 proteins, Bet v 1 homologue**
- Heat labile protein

**Profilins**
- Highly cross-reactive, present in most plants

**Storage proteins**
- Proteins found in seeds
- Often stable and heat resistant
- Often associated with systemic and severe reactions

**LTP, lipid transfer protein**
- Stable to digestion and heat
- Often associated with systemic and severe reactions in addition to OAS

**CCD, cross-reactive carbohydrates**
- Highly cross-reactive, present in most plants
- Seldom associated with clinical symptoms

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**Serum albumin’s**
- A common protein present in different biological fluids and solids e.g cow’s milk and beef, egg and chicken
- Cross-reaction between albumin from different anima species are well known. Cat and dog, cat and pork.

**Enzymes**
- Including Bromelin and Pepsin

**Moulds**
- Limited cross reactivity
- Useful for specific diagnosis

**Others**
- Tropomyosin- A class of highly conserved Protein, heat stable
- **Egg ovomucoid** - Very heat stable and enzyme resistant

**Venoms**
- Determine venom allergy in relation to specific species for immunotherapy purposes
PR10- Proteins - *Bet v 1*-homologous allergens

- Heat labile protein
- Often associated with local symptoms
- Often associated with allergic reactions to fruits and vegetables in northern Europe

<table>
<thead>
<tr>
<th>Bet v1</th>
<th>Pru p 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cor a 1</td>
<td>Ara h 8</td>
</tr>
<tr>
<td>Mal d 1</td>
<td>Gly m 4</td>
</tr>
</tbody>
</table>
Profilins - *Bet v 2-homologous allergens*

- Highly cross-reactive, present in most plants
- Seldom associated with clinical symptoms but may cause demonstrable or even severe reactions in a small minority of patients

<table>
<thead>
<tr>
<th></th>
<th>Bet v 2</th>
<th>Phl p 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pru p 4</td>
<td>Hev b 8</td>
<td></td>
</tr>
</tbody>
</table>
LTP’s — non specific Lipid Transfer Proteins

- Stable to digestion and heat
- More associated with allergic reactions to fruits and vegetables in southern Europe
- Often associated with systemic and severe reactions in addition to OAS

- Fruits
- Vegetables
- Nuts
- Weed pollen

<table>
<thead>
<tr>
<th>Pru p 3</th>
<th>Ole e 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cor a 8</td>
<td>Ara h 9</td>
</tr>
<tr>
<td>Par j 2</td>
<td>Art v 3</td>
</tr>
</tbody>
</table>
Storage Proteins

- Proteins found in seeds and nuts
- Often stable and heat resistant
- Often associated with systemic and severe reactions

- Legumes
- Nuts
- Grains and seeds

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 S albumin, Ara h 2</td>
<td>Gliadins</td>
</tr>
<tr>
<td>7 S globulin, Ses i 3</td>
<td>Alpha amylase inhibitors</td>
</tr>
<tr>
<td>11 S globulin, Gly m 6</td>
<td>Vicilin, Jug r 2</td>
</tr>
</tbody>
</table>
CCD’s — Cross Reactive Carbohydrate Determinants

• Many allergen proteins are Glyco-proteins
• And therefore share similar glyco-structures such as CCDs
• CCD’s therefore can be highly cross Reactive across different plant and animal species
• Broad sensitisation patterns can be caused by CCDs
• 2 ImmunoCAPs to consider;
  • o214 MUXF3 CCD and nAna c 2, Bromelin Pineapple

• Plants
• Venom
• Dust mite

Carbohydrate Chain
Rule of Thumb

Profilin’s and PR10 proteins

- Highly cross reactive (PR 10 especially to Birch)
- Often associated with less serve reactions e.g. OAS

nsLTP’s and Storage Proteins

- Associated with more severe reactions
- More heat/digestive enzyme resistant and therefore can be more often associated with OAS and well as digestive problems
ALLERGY IN CLINICAL PRACTICE

Risk- For identification of patients at risk for severe food reactions

• Should we be challenging a given patient at this point in time?
• Home challenge?
• Epipen?
• Allergy persistence?

Ara h 1,2 and 3 (peanut), Gal d 1, ovomucoid

Allergen components are the foundation of accurate allergy diagnosis and appropriate follow-up.
ALLERGY IN CLINICAL PRACTICE

Ruling Out Cross Reactivity

• Cross Reactive Markers from suspect allergen
  Proflins, PR10’s, CCD’s etc

• Use suspected specific allergen markers (often of risk)
  e.g. Ara h 2 (Peanut)

• Take into account whole allergen specific IgE levels such
  as Birch and Grass
Peanut

Peanut Allergen Components

Ara h 1  Storage proteins
Ara h 2  Storage proteins
Ara h 3  Storage proteins
Ara h 5  Profilin
Ara h 8  PR-10
Ara h 9  LTP

Ara h1-3 are the major peanut allergens\(^1\)

Peanut Allergy in the UK in 3 -5 year olds

P<0.001

Hourihane, 2007
Standard tests over-diagnose peanut allergy

As many as 4 in 5 children diagnosed with peanut allergy on standard skin-prick tests alone may not be truly allergic to peanuts, researchers have found. A new, more specific test could help to cut the numbers wrongly diagnosed.

Nut allergy ‘myth’ is cracked

THOUSANDS of children who were told they may have a peanut allergy could be given the all-clear thanks to Manchester scientists.

About one in 10 children who are tested using existing technology are advised to avoid eating food with nuts.

Fewer people have real peanut allergy than previously thought

Scientists have developed a new more accurate test for peanut allergy after finding that eight out of ten children who previously tested positive were not in fact allergic to the nut.

New test predicts whether kids will have nut allergies

A simple blood test which predicts whether a child has a potentially fatal peanut allergy has been
MAAS Peanut Study

MAAS
1085 born into unselected population based cohort

1029 attended 8-year Follow-up

110 children were peanut sensitized

11,8% were peanut sensitised

81 Oral Food Challenges

The prevalence of clinical peanut allergy among sensitised subjects 22,4%

Inclusion criteria
- SPT ≥ 3mm
- sIgE ≥ 0.2 kUa/l
- Suggestive history

Nicolaou, Woodcook, Custovic et al. JACI 2010
MAAS Study Statistics

• 10% of 8 year old children in the UK are peanut sensitised
• Only 2% have true peanut allergy
• Sensitised patients are more likely to have hay fever and less likely to have asthma, eczema or other food allergies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Peanut Sensitised and tolerant</th>
<th>Peanut Sensitised and Allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara h 2 Level (median fold increase to control group*)</td>
<td>0.28</td>
<td>6.06</td>
</tr>
<tr>
<td>Serum Specific IgE average Peanut</td>
<td>0.96 kUA/L</td>
<td>26.47 kUA/L</td>
</tr>
<tr>
<td>Serum Specific IgE average Grass</td>
<td>74.70 kUA/L</td>
<td>6.93 kUA/L</td>
</tr>
</tbody>
</table>

*data based on micro array analysis micro-array multiplex
Conclusion MAAS Peanut study

- The majority of children considered peanut-sensitised on the basis of standard tests do not have peanut allergy
- Ara h 2 was the most important predictor of clinical peanut allergy

Clinical implications
Measurement of IgE response to major peanut allergen Ara h 2 is more useful in predicting clinical allergy than currently used skin or blood tests
A Novel Immunoassay Using Recombinant Allergens Simplifies Peanut Allergy Diagnosis

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A.-C. Vilain\textsuperscript{d} M.-O. Cousin\textsuperscript{d} A. Decoster\textsuperscript{e} J.-M. Renaudin\textsuperscript{a, b} C. Astier\textsuperscript{a}
J.-M. Monnez\textsuperscript{c} P. Vallois\textsuperscript{c} M. Morisset\textsuperscript{a} D.-A. Moneret-Vautrin\textsuperscript{a} M. Brulliard\textsuperscript{b}
V. Ogier\textsuperscript{b} M.-C. Castelain\textsuperscript{d} G. Kanny\textsuperscript{a} B.E. Bihain\textsuperscript{b} S. Jacquenet\textsuperscript{b}

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Conreanu et al - A novel immunoassay using recombinant allergens simplifies peanut allergy diagnosis Int Arch Allergy Immunol 2011;154; 216-226
Codreanu peanut study 2010

Patients enrolled at 2 centres, children and adults (3-18 years)

Peanut-allergic patients included based on DBPCFC and OFC

Peanut Allergy 166

Pollen sensitised without peanut allergy (eating peanuts without symptoms) 61

Healthy controls; 10 non-atopic individuals

Patients tested for specific IgE: whole peanut extract (f13), Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 7, Ara h 8

Codreanu et al - A novel immunoassay using recombinant allergens simplifies peanut allergy diagnosis Int Arch Allergy Immunol 2011;154; 216-226
Codreanu peanut study 2010

• Whole Peanut extract (f13) offers excellent sensitivity – 100% using 0.35 as cut off but specificity is much lower (20%)
• 79% of pollen sensitised patients showed IgE binding to f13 peanut and 69% had IgE to Ara h 8 but without peanut symptoms.
• Whole peanut extract contains cross reactive allergen components i.e. proflins, PR-10s CCD’s etc in addition to genuine peanut allergens
• rAra h 2 was the best individual marker with sensitivity 93% and specificity 96% when using a cut off of 0.23 ku/l
• Using the “Sampson” cut off value (15 ku/l) whole extract, f13, provided a sensitivity of 50% (leaving 50% of patients at risk of accidental exposure)

Recommendations
• Caution when a physician is confronted with very low IgE peanut result (History)
• Most peanut allergy can be diagnosed with the help of a simple blood test (Peanut + rAra h 2)
• The DBPFC should no longer be a mandatory diagnostic procedure
Assessment of peanut allergy

Peanut (Specific IgE) + Ara h 2 + Ara h 8

- Peanut: neg
  - Ara h 2: neg
  - Ara h 8: neg
  - Low risk for severe reactions to peanut
  - Further testing: In geographical areas where birch is common consider testing for Ara h 8

- Peanut: pos
  - Ara h 2: neg
  - Ara h 8: pos
  - Risk for severe reactions to peanut
  - Further testing: Risk grading:
    - Ara h 1
    - Ara h 3
    - Ara h 9
    - Birch

- Peanut: pos
  - Ara h 2: pos
  - Ara h 8: neg
  - High risk for severe reactions to peanut
Egg – Ovomucoid Allergen Component

- Allergy to egg is generally agreed to be one of the most common causes of food allergy in infants and young children.
- IgE antibodies to egg white in infancy are a good indicator of atopy and predict the development of disease later in life\(^1\)
- Common clinical decision - reintroducing cooked egg back into the diet

**Major Egg Allergen Components\(^3\)**

- Gal d 1 Ovomucoid
- Gal d 2 Ovalbumin
- Gal d 3 Conalbumin
- Gal d 4 Lysozyme

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Ovomucoid

- Consists of 3 domains containing 3 disulfide bridges each (total 9 SS-bridges)
- Highly glycosylated
- Very heat stable and resistance to proteases
- Relative resistant to enzymatic degradation
- High specific IgE concentrations to ovomucoid is associated with persistent egg allergy \(^1,2,3,4\)

1. Bernhisel-Broadbent et al. JACI 1994,
2. Urisu et al. IAAI 1999
3. Takagi et al. IAAI 2005
Plain Speaking....

• Patients who are positive to Ovomucoid demonstrate that they can not even tolerate cooked egg and therefore have not out grown their egg allergy. They may have persistent egg allergy.

• Patients who come up negative to Ovomucoid can tolerate cooked egg.
Assessment of egg allergy

Egg white (Specific IgE) + Ovomucoid

- Egg white: neg
  Ovomucoid: neg
  Low risk for clinical reactions to egg

- Egg white: pos
  Ovomucoid: neg
  Risk for clinical reactions to egg

- Egg white: pos
  Ovomucoid: pos
  High risk for clinical reactions to egg

Absence of IgE antibodies to ovomucoid indicates tolerance to ingestion to baked egg

Increased risk for persistent egg allergy
Ovomucoid Study – Ando et al 2008

• 180 Patients, DBPFCs - Raw Egg White, Cooked Egg
• Investigated the clinical predictability of the three egg white component tests egg white, ovomucoid and ovalbumin
• Ovomucoid test demonstrated superior predicative values for cooked egg (than the other tests)
• Decision points- positive predicative value 10.8 kUA/l (PPV 95%) and negative predicative value at 1.2 PV kUA/l (PPV 95%)

Conclusions – Quantitative decision points for both egg white and ovomucoid will be useful in the diagnosis of egg allergy
IgE ImmunoCAP ISAC

The tool for the future in allergy diagnostics

Available today!
ImmunoCAP ISAC

- Immuno Solid-phase Allergen Chip - ISAC
- Covers 47 Food allergens + Others allergens
- Network of Instruments UK and IRLD
  - Private and NHS
- Marker allergens (specific and cross reactive)
- Only 20 µl of serum needed
- Detection of IgE, IgG, IgG4 antibodies is possible
- Performance similar to standard ImmunoCAP
Where does ImmunoCAP ISAC fit in?

- Remove subjectivity
- Provide a complete patient profile
- Patients with unidentified allergy
  - Anaphylaxis
  - Rule out as many allergens as possible
- Cost effective method if having to access multiple components
- Determining and monitoring immunotherapy
1. Summary of positive allergen-specific IgE results

<table>
<thead>
<tr>
<th>Species specific components</th>
<th>Unit</th>
<th>ISU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass pollens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bermuda Grass</td>
<td>nCym d 1</td>
<td></td>
</tr>
<tr>
<td>Timothy Grass</td>
<td>rPhl p 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rPhl p 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rPhl p 6</td>
<td></td>
</tr>
<tr>
<td>Tree pollen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birch</td>
<td>rBet v 1</td>
<td>27</td>
</tr>
<tr>
<td>Animal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>rFle d 1</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>rFle d 4</td>
<td>1.5</td>
</tr>
<tr>
<td>Dog</td>
<td>rCan f 1</td>
<td>2</td>
</tr>
<tr>
<td>Mould</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternaria</td>
<td>rAlt a 1</td>
<td>9.4</td>
</tr>
<tr>
<td>Milts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. pteronyssinus (HDM)</td>
<td>rDer p 2</td>
<td>11</td>
</tr>
<tr>
<td>D. farinae (HDM)</td>
<td>rDer f 2</td>
<td>14</td>
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<tr>
<td>Components with limited cross-reactivity</td>
<td></td>
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<tr>
<td>PR-10 protein</td>
<td></td>
<td></td>
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<tr>
<td>Birch</td>
<td>rBet v 1</td>
<td>27</td>
</tr>
<tr>
<td>Apple</td>
<td>rMal d 1</td>
<td>2</td>
</tr>
<tr>
<td>Peach</td>
<td>r Pru p 1</td>
<td>1.4</td>
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<tr>
<td>Cross-reactive components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profilin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birch</td>
<td>rBet v 2</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy


1Rheumatology Research Laboratory, 2Department of Paediatric Medicine—Allergy Unit, 3Clinical Chemistry and 4Epidemiology, I.R.C.C.S. Children’s Hospital ‘Bambino Gesù’, Rome, Italy

Summary

Background The food challenge test (FCT) is the gold standard for the diagnosis of food allergy. This procedure is time consuming, costly and can induce potentially severe symptoms. An ideal in vitro test should allow to avoid the FCT.

Objective To assess the clinical performance of microarray for specific IgE (sIgE) detection in children with challenge-proven/excluded cow’s milk (CM) or hen’s egg (HE) allergy.

Methods One-hundred and four children with suspected sIgE-mediated hypersensitivity to CM or HE were studied. In all patients, skin prick test, ImmunoCAP, microarray and FCT were performed.

Results The microarray components Bos d 8 for CM (27/58 patients) and Gal d 1 (20/46 patients) and Gal d 2 (24/46) for HE were the most frequently recognized allergens. Using the FCT results as the reference parameter, sIgE to Bos d 8 and Gal d 1 had the highest area under the curves. These were not significantly different from those obtained using the ImmunoCAP. Use of 95% clinical decision points (CDP) for sIgE to Bos d 8 and Gal d 1 resulted in higher negative predictive values (78% and 79%, respectively) than those obtained with the ImmunoCAP (57% and 59%).

Conclusions Our results show that in children with suspected CM or HE allergy, the microarray has a good ability to predict the FCT results. In a clinical application perspective, the microarray could be used as a second-level assay, if the ImmunoCAP sIgE is < 95% CDP. This approach would lead to a decrease in the number of the FCT to be performed, as well as of positive FCTs with a subsequent decrease in severe reaction risk.

Keywords cow’s milk allergy, food challenge test, hen’s egg allergy, microarray, specific IgE

Submitted 16 February 2010; revised 18 May 2010; accepted 25 May 2010.
Molecular Allergology is breakthrough science that enables quantification of IgE antibodies to single allergen protein components at a molecular level. These new diagnostic tools provide unique, previously unavailable information:
- sensitisation pattern
- clinical risk for severe reactions
- cross-reactivity between allergens
- guide in the selection of optimal treatment options for each patient
# Hazelnut

## Hazelnut allergen components

<table>
<thead>
<tr>
<th>Protein Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cor a 1</td>
<td>PR-10</td>
</tr>
<tr>
<td>Cor a 2</td>
<td>Profilin</td>
</tr>
<tr>
<td>Cor a 8</td>
<td>LTP (Lipid transfer protein)</td>
</tr>
<tr>
<td>Cor a 9</td>
<td>Storage protein (11S globulin-like protein)</td>
</tr>
<tr>
<td>Cor a 11</td>
<td>Storage protein (7S vicilin-like protein)</td>
</tr>
<tr>
<td>Cor a 12</td>
<td>Oleosin</td>
</tr>
<tr>
<td>Cor a 13</td>
<td>Oleosin</td>
</tr>
<tr>
<td>Cor a 14</td>
<td>Storage protein (2S albumin)</td>
</tr>
</tbody>
</table>
Hazelnut

• Severe nut allergy,
  • Cor a 8 sensitisation
    • May be cross-reactive allergy with fruits or other nuts
  • Cor a 9 sensitisation
    • May be cross-reactive allergy with nuts, peanuts and soy

• Mild nut allergy,
  • Cor a1 sensitization
    - Often associated with birch pollen allergy
    - Close homology between Bet v 1 and Cor a 1 (80%)
Suspicion of Hazelnut Allergy?

Hazelnut (f17) + Cor a 8 (f425)
Test with ImmunoCAP® Allergen

Hazelnut: neg
Cor a 8: neg

Very low risk for severe reactions to hazelnut

Hazelnut: pos
Cor a 8: neg

Risk for severe reactions to hazelnut

Hazelnut: pos
Cor a 8: pos

High risk for severe reactions to hazelnut

Recommendations for further testing:
Risk grading:
Cor a 1 (f428)  ●●
CCD (Ro214)  ●