

Oral Allergy Syndrome: A Confluence of Immunology and Phylogeny

by

Merle K. Heidemann, Mike S. Taylor, Amanda Storm, Cassie Dresser-Briggs, Alexa Warwick, and Peter J.T. White

Objectives

Upon completion of this case study, you should be able to:

- Explain the symptoms of allergic reactions in terms of cell biology (immune system cells).
- Describe the molecular features of cross reactivity.
- Build phylogenetic trees using morphological data.
- Build phylogenetic trees using molecular data and interpret two kinds of phylogenetic trees.

Part I – Immunology

Sam had a history of allergic reactions, including reactions to various plant pollens. Birch pollen elicited a particularly strong reaction, causing him annoying sneezing fits and a sore throat. As he grew to adulthood, he discovered that he was also variably allergic to common foods, including some raw fruits and vegetables, as well as most nuts.

Sam was puzzled by his recent food allergies. Also puzzling was the variability in his reactions. He reacted strongly to some foods; others resulted in only a mild itchy throat. He wondered, *What exactly causes allergic reactions?*

Sam was determined to figure out how and why he reacted to birch pollen and later became allergic to other plant-based food. He also hoped this information might help him avoid other foods that might cause him allergies.

First, Sam decided he needed to know something about the cellular bases of allergic reactions. He knew it had something to do with the immune system. He did some basic research on the Internet and here's what he found:

Allergens are bits of protein from an innocuous foreign substance, such as pollen or food. When these particular protein bits enter a person's body, they lead to the release of histamines that open the gates to an immune response by making capillaries leaky to white blood cells and some specialized proteins.

Symptoms of a relatively mild allergic reaction include hives; itchy skin and throat; sneezing, wheezing and/or coughing; swelling of throat; and gastrointestinal distress. Symptoms that result from a more serious reaction include dizziness, weak pulse, shock, and worst of all, anaphylaxis, a hypersensitive condition resulting in extreme response. In severe cases, allergic reactions may even lead to death.

Histamines are released from specialized cells called mast cells. This release is controlled by a protein called immunoglobulin E (IgE), which is produced by a particular kind of B lymphocyte. B lymphocytes are key cells in the vertebrate adaptive immune response.

This information was a useful starting point for Sam, but it left many questions unanswered.

Questions

1. What is the job of the adaptive immune response in humans?
2. How do B lymphocytes function in the adaptive immune system response?
3. What is the normal (non-allergenic) function of an IgE antibody and how does it accomplish this?
4. What is the non-normal (allergenic) function of an IgE antibody and how does it accomplish this?
5. How does the release of histamine lead to allergic symptoms?

Part II – A Confluence of Immunology and Phylogeny

Next, Sam’s research found that the symptoms of food allergic reactions are often related to the gastrointestinal system. They are due to soy products, chicken eggs, cow’s milk, peanuts, tree nuts, wheat, shellfish and fish. These allergies generally develop in infants and children. The allergens are various food glycoproteins that remain stable in the gut. Sometimes children grow out of these allergies, which is often the case with cow’s milk.

Some adults develop oral allergy syndrome, OAS, also called “pollen-food allergy syndrome.” They experience an itchy mouth and tongue, and swelling lips when eating raw fruits and veggies, as well as some tree nuts. This reaction is not considered a true food allergy, but a pollen allergy. It develops most commonly in adults who also have hay fever (pollen allergy).

OAS allergens are close cousins of proteins associated with certain types of pollen. For example, if you are allergic to birch pollen, like Sam, you could also experience OAS to apples and pears; peaches, cherries and plums; almonds and hazelnuts; kiwi; celery; carrots, etc.

Birch Pollen and Bet v 1

The system for naming plant allergens is based on the first three letters of the genus name, followed by the first letter of the species name and the order in which the allergen was discovered. “Bet v 1” was the first protein found on the pollen of the birch tree, *Betula verrucosa*.

Bet v 1 is thought to be a special type of protein that can protect plants by attacking the cell walls of pathogenic fungi and bacteria. Bet v 1 has a “cavity” that binds to many ligands (i.e., other molecules that may react to Bet v 1), including IgE molecules produced by people. When this binding happens in humans, it leads to the release of histamines and an allergic reaction ensues.

Bet v 1 protein is the best-known member of the Bet superfamily and is found across all groups of plants, animals and fungi. A single Bet v 1 family, with lots of variants, is found in plants; most of these variants are thought to be important for defense against pathogens. These Bet v 1 homologues (meaning they share common ancestry) are found associated with a wide variety of common fruits and vegetables.

People who are sensitive to the Bet v 1 protein found on birch pollen become sensitive to the analogous proteins (i.e., proteins that have a similar shape) that are found across a wide array of plant species. An example is Act d 11 found in kiwi. While the *Act d 11* and *Bet v 1* genes are not identical in terms of their DNA sequences, once the amino acid chain resulting from each gene is folded into a protein they end up having a very similar three-dimensional shape (see Figure 1). Because of this similar structure, an immunoglobulin E antibody that reacts with the Bet v 1 protein to produce an allergic response may also react with an Act d 11 protein to produce the same allergic symptoms. In other words, Act d 11 is “cross reactive” with IgEs that react to Bet v 1 to initiate histamine release and the subsequent misery of an allergic reaction.

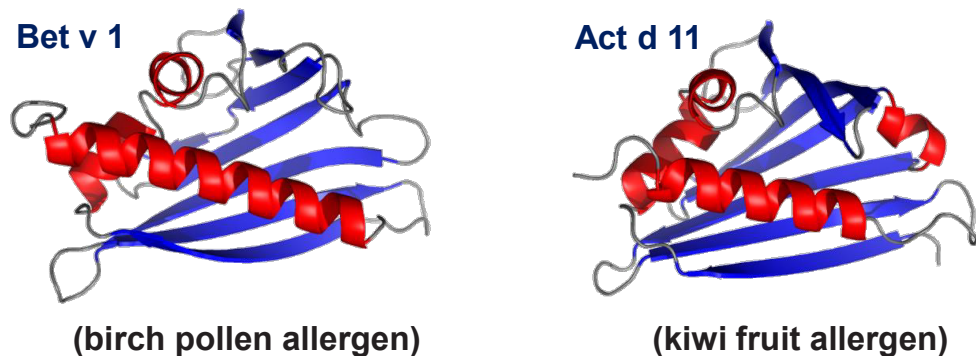


Figure 1. Comparison of the three-dimensional structure of Bet v 1 and Act d 11 proteins.
Credit: Maksymilian Chruszcz, University of South Carolina. Used with permission. <<http://artsandsciences.sc.edu/chemgroup/chruszcz/food-allergens>>.

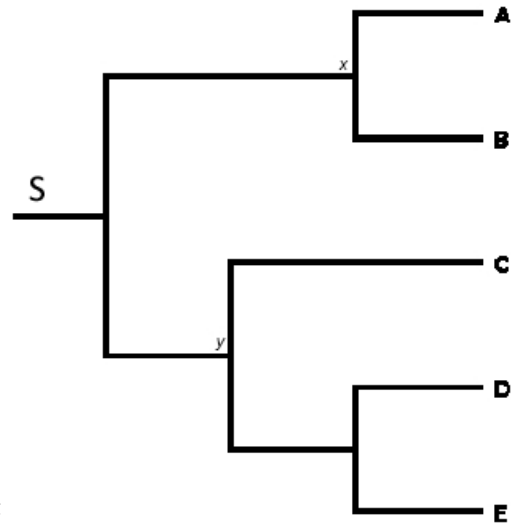
Part III – Phylogeny

Sam wondered whether biologists could use known differences and similarities in Bet v 1 family plant proteins to map and predict the severity of allergic reactions and evolutionary relationships. With a little research, Sam determined the answer was yes; differences in plant proteins could be used to generate phylogenetic trees! Would doing so help him determine which foods he should avoid? But what is a phylogenetic tree and what does it indicate?

Before answering the questions below, you will need to become proficient at reading and understanding phylogenetic trees. In order to do this, access the “Evolutionary trees: a primer” found on the *Understanding Evolution* website here: <https://evolution.berkeley.edu/evolibrary/article/0_0_0/evotrees_primer_01>. Work through the seven modules in this primer (i.e., “What is a tree,” “How to read trees,” “Understanding evolutionary relationships,” etc.) and summarize what you have learned.

Questions

1. What do x , y , A , B , C , D , and E represent in the diagram to the right? What is the “stem” (labeled with an “S”) in the diagram?



2. What are shared derived traits? What do these traits indicate about ancestral relationships?

3. What does it mean to “infer” a common ancestor? What does this “inference” look like on a phylogenetic tree?

4. What are the three basic steps to producing a phylogenetic tree?

Part IV – A Flowering Plant Phylogeny

Sam now had a basic understanding of two aspects of his problem that interested him: immunology and the ways to think about the evolutionary relationships among species or groups of species.

A trip to an allergist confirmed that Sam had OAS, more correctly known as pollen-food allergy syndrome. Sam’s variable reactions were due to different members of the plant Bet v 1 family of proteins. Sam wondered about his variable reactions. Being a plant geek, he spent a couple of hours mapping his responses to food on a plant phylogenetic tree generated by the American Phylogeny Group and generated a tree similar to Figure 2.

Sam could eat plants that are from the “green” plant orders; he couldn’t easily eat those from the “red” orders. Black lines indicate orders that do not have plants that people consume.

Questions

1. Based on this phylogenetic tree, predict which raw fruits and vegetables would likely cause the most severe reactions and which are less bothersome for Sam.
2. The orders Rosales and Apiales (rosids and asterids) are not closely related, yet Sam is allergic to members of both orders. Give a plausible explanation.
3. Why can Sam eat an apple pie but not a raw apple?

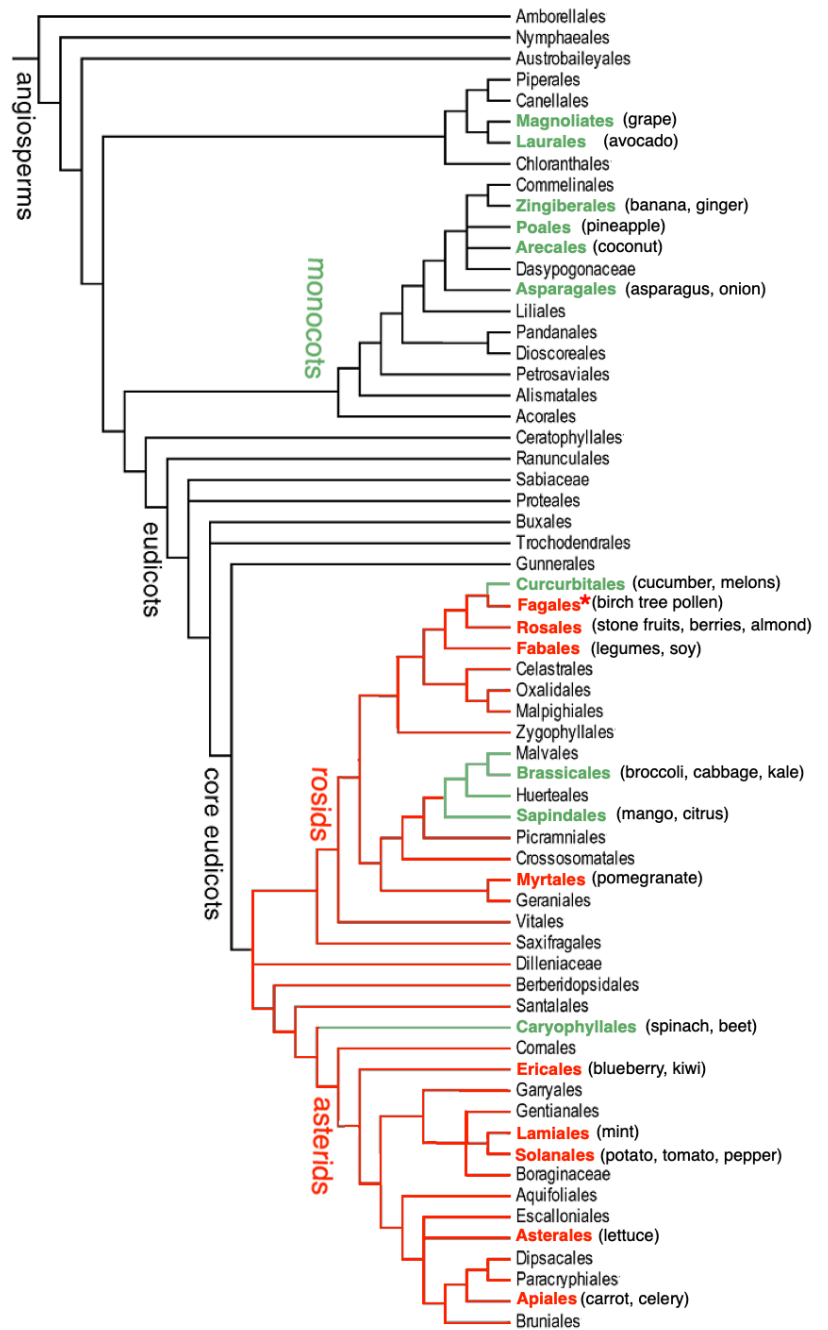


Figure 2. Phylogenetic tree adapted from “An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG IV” by The Angiosperm Phylogeny Group: M. W. Chase, M. J. M. Christenhusz, M. F. Fay, J. W. Byng, W. S. Judd, D. E. Soltis, D. J. Mabberley, A. N. Sennikov, P. S. Soltis. *Botanical Journal of the Linnean Society* 181(1): 1–20, <https://doi.org/10.1111/boj.12385>.

Part V – Analyzing Amino Acid Sequences

After determining where problematic foods were found in a large-scale plant phylogenetic tree, Sam wanted even more information about those that bothered him. He decided to look up the proteins responsible for his responses to fruits and vegetables, knowing that they were related to Bet v 1. He guessed that those that were the worst for him would be more closely related than those that weren't so bad. The sequences he found are shown below.

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>Celery
MGVQTHVLELTSSVSAEKIFQGFVIDVDTVLPKAAPGAYKSVEIKGDGGPGTLKIITLP
>Carrot
MGVQKHEQEITSSVPAEKMGHGLILDIDNILPKAAPGAYKNVEIKGDGGVGTIKHITLP
>Parsley
MGAVTTDVEVASSVPAQTIYKGFLLDMDNIIPKVLPAIKSIEIISGDGGAGTIKKVTLG
>Kiwii
MGAITYDMEIPSSISAEMFKAFVLDGDTIIPKALPHAITGVQTLLEGDGGVGTIKLITFG
>Cherry
MGVFTYESEFTSEIPPPRLFKAFLVDADNLVLPKIAPQAIKHSEILEGDGGPGTIKKITFG
>Peach
MGVGTYESEFTSEIPPPRLFKAFLVDADNLVLPKIAPQAIKHSEILEGDGGPGTIKKITFG
>Pear
MGLYTFENEFTSEIPPPRLFKAFLVDADNLIPKIAPQAIKHAEILEGNGGPGTIKKITFG
>Strawberry
MGVFTYESEFTSVIPPPKLFKAFLVDADNLIPKIAPQAVKSAEIEGDGGVGTIKKIHLG
>Raspberry
YTSVIPPPKLFKAFLVDADNLIPKIAPQAVKSVEIEGDGGVGTVKKIHLG
>Apple
MGVFNYTEFTSVIPPARLNFVLDADNLIPKIAPQAVKSAEILEGDGGVGTIKKINFG
>Apricot
MGVFTYTEFTSVIPPEKLFKAFILDADVLIPKVAPTAVKGTEILEGDGGVGTIKKVTFG
>Birch
MGVGNYETETTSVIPAAARLFKAFILDGDNLFKVPAPQAISVENIEGNGGPGTIKKISFP
>Soybean
MGVFTSESEHVSPVSAAKLYKAIVLDASNVPPKALPNFIKSVEITIEGDGGPGTIKKLTLA
>Potato
MGVTSYLETTPVAPTRLFKALVVDSDNLIPKLMQVKNIEAEGDGSIKKMTFV
>Tomato
MGVTTYTHEDTSTVSPNRLFALVIDGDNLIPKLMNVKNVETEGDGSIKKINFV

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Task

- Go to: <<http://www.phylogeny.fr/>>.
- Click on “one click” mode.
- Copy the entire set of amino acid sequences into the box, beginning with the > sign in front of “celery.”
- Click on the “Submit” button. This tool automatically aligns and analyzes the sequences. The “run” will happen quickly.
- Download the tree from the website and answer the questions below.

Questions

1. What does the scale on the bottom of the tree indicate?
2. What do the numbers in red mean?
3. What is the relevance of the length of the branches?
4. Using the overall angiosperm phylogenetic tree, what would be the common ancestor to the tree you generated?
5. Look up the orders and families in which each analyzed food item belongs. Which order and family would you predict are most problematic (most allergic symptoms) for Sam and why?
6. What is their common ancestor?
7. Does the generated molecular phylogenetic tree always line up with the general angiosperm phylogeny?

Back to Sam and the Big Question

When Sam was done with his research on both immunology and phylogeny, he took some time to process the information. His big question to answer was:

What is the relationship between the likelihood and severity of his OAS responses to fruits and vegetables and their phylogenetic relationships to birch pollen and each other?