Science News
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September 30, 2017

Genes Foretell Flu Shot Response

SOCIETY FOR SCIENCE & THE PUBLIC

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About the Issue

Science News **article(s):** "Genes foretell flu shot response"

Readability score: 11.9

Science News for Students **article(s):** "Genes may predict how well the flu vaccine will work in young people"

Readability score: 7.7

The article "Genes foretell flu shot response" describes how measuring the activity of a small number of genes can predict how well a young person's immune system will respond to a flu vaccine. Students can focus on details reported in the article, follow connections to earlier articles about influenza and its vaccines, and explore cross-curricular connections to other major science topics such as molecular biology and immunology. In a related activity, students can work in groups or independently through guided questions to better understand influenza's genomes and why the virus mutates.

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Article-based observation: Questions focus on the details of a recent study that identified a set of predictive genes for determining the effectiveness of flu vaccines.

Quest through the archives: Use this short section to explore other articles about flu viruses and vaccines as reported by *Science News* since 1924.

Cross-curricular discussion:

> **Biological Sciences** questions address DNA, RNA, replication, transcription and translation, as well as the basic principles of the immune system and vaccines.
>
> **Chemical Sciences** questions focus on the difference between physical and chemical changes that pertain to DNA and chemical adjuvants that are added to many vaccines to try to maximize an individual's immune response.
>
> **Engineering and Experimental Design** questions deal with the design of similar studies for other age groups and other ways measuring or manipulating gene expression might be useful.

Activity: Catching the flu

> **Purpose:** To gain a better understanding of influenza, its genomes, mutations and vaccines.
>
> **Procedural overview:** This guided research activity encourages the exploration of public data and information to learn more about influenza's genes and proteins, how flu vaccines are made and nine human genes that predict how well a flu vaccine will work in young people.
>
> **Approximate class time:** 40 to 60 minutes.

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Standards

Next Generation Science	Common Core ELA
Motion and Stability: Forces and Interaction: HS-PS2-6	Reading Informational Text (RI): 1, 2, 4, 5, 7
From Molecules to Organisms: Structures and Processes: HS-LS-1, HS-LS1-2, HS-LS1-3, HS-LS1-4, HS-LS1-6	Writing (W): 1, 2, 3, 4, 6, 7, 8, 9
Heredity: Inheritance and Variation of Traits: HS-LS3-1, HS-LS3-2	Speaking and Listening (SL): 1, 2, 4, 5, 6
Biological Evolution: Unity and Diversity: HS-LS4-1, HS-LS4-2, HS-LS4-3, HS-LS4-4, HS-LS4-5	Reading for Literacy in Science and Technical Subjects (RST): 1, 2, 3, 4, 5, 7, 8, 9
Engineering Design: HS-ETS1-1, HS-ETS1-2, HS-ETS1-3	Writing Literacy in History/Social Studies and Science and Technical Subjects (WHST): 1, 2, 4, 7, 8, 9

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Article-Based Observation: Q&A

1. Summarize the article in one sentence.

Possible student response: For people 35 and under, measuring the activity of certain genes can predict how well flu vaccines will work.

2. Explain what the author means by a genetic "crystal ball." How does the crystal ball work and what group of people does it work for?

Possible student response: The genetic "crystal ball" is a metaphor for a set of nine genes that researchers in a recent study associated with a strong immune response to flu vaccines in people age 35 and under. When these genes were identified as highly active in individuals before a flu vaccination was given, high levels of antibodies were produced after the vaccination was administered. In other words, these genes act like a "crystal ball" because they can predict how well these individuals' immune systems will respond to flu vaccines.

3. What research question did computational immunologist Purvesh Khatri and his colleagues explore? How did they go about answering it in their study?

Possible student response: Purvesh Khatri and his colleagues wondered if a specific immune state was associated with an effective response to flu vaccines. They looked for a common genetic signal in blood samples from 175 people with different genetic backgrounds, from different locations in the United States and who received flu vaccines in different seasons. After identifying the set of predictive genes, the team used another collection of 82 samples to confirm that those genes accurately predicted a strong flu response.

4. What result did researchers find when they tried to identify a similar set of genes in people age 60 and older? Why is it more difficult to predict the response of older people to the flu vaccine? How could the design of a new study solve this difficulty?

Possible student response: The researchers tried but failed to identify a similar set of predictive genes for people who were age 60 or older. Older people are even more diverse in how they respond to flu vaccines than younger people. The article suggests it may take a larger number of samples to identify genes in older people that are linked to a strong immune response.

5. Why has it been difficult to predict the success of a flu vaccination?

Possible student response: Individuals and certain groups of individuals have unique responses to flu vaccinations. Scientists currently do not have a detailed understanding of what factors ensure that a person will have a strong immune response to a vaccine. There are many different strains of flu virus, each requiring a separate vaccine. Companies that make flu vaccines must predict up to a year in advance what three or four flu strains will likely be circulating the following flu season and mass produce vaccines for the right strains. Sometimes these predicted vaccines are widely effective and sometimes they are not.

6. Were all nine genes previously linked to immune function? What other roles do these genes play in the body?

Possible student response: Some of the genes were already known to be related to the immune system, but others were not. The nine genes code for proteins that have various jobs, including directing the movement of other proteins and providing structure to cells.

7. In what ways can the results of this study benefit future studies in immunology?

Possible student response: (1) Scientists can now study how those nine genes promote a strong immune response. (2) The activity of those nine genes can be used to predict how well a flu vaccine might work for a specific person. (3) Researchers might find ways to boost the activity of those nine genes to provoke a stronger immune response in people for whom the flu vaccine would otherwise not be very effective.

8. Approximately how many flu illnesses did vaccination prevent during the 2015–2016 season?

Possible student response: The U.S. Centers for Disease Control and Prevention estimates that vaccination prevented 5.1 million flu illnesses in the 2015–2016 season.

9. Did particular flu strains that were vaccinated for affect the results of the study? Would the approach used in this study work for vaccines for other viruses?

Possible student response: The same nine genes predicted whether people age 35 or younger would produce high levels of antibodies in response to all flu vaccines tested. It is possible that this study's approach would work for vaccines against different viruses, but the scientists only tested people's responses to flu vaccines. More research is required to answer that question.

10. Article-based opinion question: Are you planning to get the flu vaccination this year? Why or why not?

Possible student response: Yes, I plan to get the flu vaccine this year — it could potentially help protect me against the most probable strains of the flu virus. No, as the article suggests, the flu vaccine doesn't produce a high immune response for everyone who gets the vaccine. So, it might not work well for me.

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Article-Based Observation: Q

Directions: Read the article "Genes foretell flu shot response" and then answer these questions:

1. Summarize the article in one sentence.

2. Explain what the author means by a genetic "crystal ball." How does the crystal ball work and what group of people does it work for?

3. What research question did computational immunologist Purvesh Khatri and his colleagues explore? How did they go about answering it in their study?

4. What result did researchers find when they tried to identify a similar set of genes in people age 60 and older? Why is it more difficult to predict the response of older people to the flu vaccine? How could the design of a new study solve this difficulty?

5. Why has it been difficult to predict the success of a flu vaccination?

6. Were all nine genes previously linked to immune function? What other roles do these genes play in the body?

7. In what ways can the results of this study benefit future studies in immunology?

8. Approximately how many flu illnesses did vaccination prevent during the 2015–2016 season?

9. Did particular flu strains that were vaccinated for affect the results of the study? Would the approach used in this study work for vaccines for other viruses?

10. Article-based opinion question: Are you planning to get the flu vaccination this year? Why or why not?

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Quest Through the Archives: Q&A

1. Specific strains of flu virus that are circulating in some years are more dangerous than others. Can you find an article about the 1918 flu strain and what made it so deadly?

Possible student response: The article "Killer findings: scientists piece together 1918-flu virus," published 10/8/2005, discusses how a group of scientists pieced together parts of the genetic instruction manual, or genome, of the 1918-flu strain from the remains of people who had died from infections caused by that strain. Another group of researchers used the partial genome to make a virus similar to the 1918-flu strain. Analyses of the lab-made virus suggested that the 1918-flu strain was similar to modern bird flu strains. They successfully infected lab animals and human cells with the reconstructed flu and studied its effects. From these experiments, the researchers identified the versions of the RNA polymerase gene and the hemagglutinin gene in the 1918 strain as being important for its virulence compared with most other flu strains.

2. Can you find an article that offers a possible alternative to administering a flu shot without a large needle?

Possible student response: The article "Getting a flu 'shot' could soon be as easy as sticking on a Band-Aid," published 8/5/2017, discusses how the flu vaccine can be delivered by a bandage on the skin instead of a large needle. The side of the bandage that touches the skin is covered with microneedles that are each a little more than half a millimeter long. Those microneedles penetrate the skin to deliver the flu vaccine and then harmlessly dissolve. The bandage could make it easier to store and deliver flu vaccines, and ensure that a greater percentage of people would get the flu vaccine each year.

3. In the article, "Genes foretell flu shot response," researchers were unable to identify genes that could improve how well flu vaccines work in people who are 60 or older. Can you find an article that explains how flu shots could be improved for the elderly?

Possible student response: The article "Elderly benefit from high-dose flu shot," published 10/4/2014, discusses a study of flu vaccines for 30,000 people 60 and older during 2010–2011. The immune system gets weaker as people age, making it harder for the immune system to "learn" from a vaccine and then protect a person from the corresponding real virus. Flu shots that contain larger amounts of flu protein than normal shots may reduce the number vaccinated people who still manage to catch the flu by about 25 percent, lab tests suggest. Side effects of the high-dose flu shot were reported to be minor.

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Quest Through the Archives: Q

Directions: After reading the article “Genes foretell flu shot response,” log in to your *Science News* in High Schools account and use the Search page to answer these questions. Make sure you adjust the filters to include articles written before 1999, if the question requires you to do so.

1. Specific strains of flu virus that are circulating in some years are more dangerous than others. Can you find an article about the 1918 flu strain and what made it so deadly?

2. Can you find an article that offers a possible alternative to administering a flu shot without a large needle?

3. In the article, “Genes foretell flu shot response,” researchers were unable to identify genes that could improve how well flu vaccines work in people who are 60 or older. Can you find an article that explains how flu shots could be improved for the elderly?

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Cross-Curricular Discussion: Q&A

Directions: After students have had a chance to review the article "Genes foretell flu shot response," lead a classroom discussion based on the questions that follow.

It would also be good to discuss with students that some of these tangential questions, questions from the other sections of this Guide and students' own questions about this or other articles might lead them to conduct their own independent research for science fair projects.

BIOLOGICAL SCIENCES

Discussion questions:

1. What are genes and viruses made of and how do they replicate?

Genes in cells — everything from bacteria to human cells — are composed of specific sequences of molecular building blocks called nucleotides in deoxyribonucleic acid (DNA). DNA typically exists as a double-stranded helix, and each strand is a polymer made of a sequence of monomer nucleotides. Nucleotides are composed of a five-carbon sugar, at least one phosphate group and a nitrogenous base: adenine (A), cytosine (C), guanine (G) or thymine (T). The two strands of DNA are complementary: Each A on one strand pairs with a T on the other strand, and each C on one strand pairs with a G on the other strand. In order for DNA to replicate, the two strands are pulled apart and then special enzymes called DNA polymerases use each existing strand as a template to form two new DNA strands. The nucleotide sequences of the new strands are complementary to, or pair with, the original template strands. The end result is two complete DNA double-stranded helices.

Some viruses store their genes as DNA (either single-stranded or double-stranded, depending on the type of virus). However, many viruses store their genes as ribonucleic acid (RNA), which may be single-stranded or double-stranded depending on the type of virus. RNA is chemically similar to DNA but less stable, so RNA degrades more rapidly than DNA. RNA is also more prone to mutation than DNA. Each RNA strand is a polymer with a sequence composed of the nucleotides adenine (A), cytosine (C), guanine (G) and uracil (U), the RNA analog of thymine. Two strands of DNA and/or RNA can be complementary: Each A on one strand pairs with a T or U on the other strand, and each C on one strand pairs with a G on the other strand.

Viruses are unable to replicate themselves, so they must infect a suitable host cell to serve as a factory to produce more copies of the virus. Most RNA viruses make their own RNA polymerase, which uses an existing RNA strand as a template to bond individual RNA nucleotides to form a new complementary strand. RNA polymerases tend to be more error-prone than DNA polymerases, which greatly increase the frequency with which RNA viruses mutate. Most DNA viruses use the host cell's DNA polymerase to replicate the viral DNA. Some viruses go through more complicated replication cycles involving strands of both DNA and RNA.

Extension prompts:

2. What do genes produce and how are their activity levels controlled?

Genes produce proteins through transcription and translation processes. The amount of proteins that genes produce, called gene expression, is controlled by specific sequences in the DNA and RNA, and by various enzymes.

In transcription, other types of polymerases copy DNA or RNA genes to produce complementary RNA strands. (In some RNA viruses, the genomic RNA itself serves as this resulting RNA strand.) Some of these RNAs include ribosomal RNA (rRNA), transfer RNA (tRNA) and messenger RNA (mRNA). They are involved in a second process called translation.

During translation, large enzymes called ribosomes, made of both rRNA and proteins, use the nucleotide sequence of mRNA to provide the code for making a protein with a specific sequence of amino acids.

3. How does the immune system specifically attack things that it recognizes should not be in your body?

White blood cells called lymphocytes help initiate an immune response. There are two main types of lymphocytes, B cells and T cells. B cells make different antibodies — proteins that bind to very specific receptors on foreign bacteria and viruses to make them ineffective. T cells have different receptors that sense specific shapes of molecules made by other cells, and kill cells that make molecules with the wrong molecular structure. Because B cells and T cells are so specific, they can only attack things that they have seen before and have learned to recognize. If they are confronted with a new substance, it usually takes your immune system a few days to initiate a response and fight off an infection — like trying all the keys on a key ring before you finally find the right one for a lock. You are generally immune to that same virus strain if you are exposed again afterward.

4. How do vaccines work?

A vaccine contains enough of a pathogen to teach your immune system how to recognize and fight the pathogen, but not enough to make you sick. The pathogen imitates an infection without causing one and initiates the production of T cells and antibodies. Some vaccines are killed versions of a pathogen — all parts of the pathogen are present so your immune system can learn to recognize it, but the pathogen is dead and therefore not able to replicate or turn on its virulence factors. Some vaccines are attenuated versions of a pathogen — the pathogen is alive but is not good at replicating itself or causing disease, so your immune system can both learn from it and kill it. Some vaccines contain just components of a pathogen — usually those parts of the pathogen's molecular exterior that your immune system would be most likely to see during a real infection. More advanced vaccines can use a harmless organism or even your own cells to produce components of a pathogen and teach your immune system to recognize those components. Some vaccines must be given in a series of doses, or given again after a certain number of years, to teach your immune system what to recognize and to make sure it remembers.

CHEMICAL SCIENCES

You may want to check out Cancer's Sweet Cloak Guide and explore Cross-curricular Q&A in the Chemical Sciences and Physical Sciences sections if you are interested in additional questions on protein composition and structure.

Discussion questions:

1. What is the difference between a physical change and a chemical change? Provide an example of each.

A physical change may alter the outward appearance of something, but it does not change the substance it is actually made of. The chemical composition of the molecules involved does not change. An example of a physical change would be water molecules changing from solid ice to liquid water to gaseous steam. The outward appearance and density of the substances change, but they remain water molecules, H_2O, throughout the process.

A chemical change alters what substance something is made of, creating one or more new substances. The chemical composition of the molecules change. During a chemical change, chemical bonds — which are formed when atoms share or exchange electrons — are created and/or broken. This changes the initial chemical molecules into new types of molecules. An example of a chemical change would be the reaction that powers many rockets, in which hydrogen molecules (H_2) and oxygen molecules (O_2) react together to form water molecules (H_2O) plus lots of energy to propel the rocket.

2. What are simple examples of physical changes and chemical changes for DNA?

One example of a physical change is pulling apart double-stranded DNA into two single strands by raising the temperature. Complementary bases in the two strands are attracted to each other by electrostatic, intermolecular attraction forces called hydrogen bonds. Hydrogen bonds are much weaker than actual chemical bonds in which electrons are exchanged or shared. Other examples of physical changes include precipitating DNA (making many DNA helices clump together to purify them in the lab), condensing DNA in the nucleus (changing how densely or loosely packed the DNA is, depending on whether it is currently needed for replication or transcription), supercoiling or kinking DNA strands and changing the DNA helix among the A, B and Z forms.

Examples of chemical changes include polymerases adding nucleotides to the end of a DNA strand, exonucleases removing nucleotides from the end of a DNA strand, endonucleases cutting a DNA strand, and mutating nucleotides within a DNA strand to create pyrimidine dimers from thymine or cytosine nucleotides, for example.

Extension prompts:

3. Many vaccines contain an adjuvant. What is that?

An adjuvant can be a chemical compound that helps the vaccine provoke a better immune response. For example, some adjuvants such as aluminum salts can generally irritate the immune system and thereby prompt it to pay more attention to the vaccine than it otherwise would. Other adjuvants such as oils or detergents can release the vaccine over a period of time or improve how the vaccine is absorbed by the body.

4. Why might it be undesirable to have too little or too much of an adjuvant in a vaccine?

With too little adjuvant, the immune system may not pay much attention to the vaccine, so the resulting acquired immunity would be less or short-lasting or would require a greater number of doses of the vaccine given over time. With too much adjuvant, the immune response to the vaccine might be too strong, causing side effects such as inflammation and fever.

ENGINEERING AND EXPERIMENTAL DESIGN

Discussion questions:

1. Why is it harder for researchers to identify genes that could predict how well older people's immune systems respond to flu vaccines? How could a study deal with that problem?

Generally the immune system and other functions get weaker as a person ages, but some people experience more decline than other people of the same age. Moreover, different people can experience different alterations in their gene expression depending on their genetic makeup and the environmental stresses to which they have been exposed throughout life. Thus, a pool of older people could include a number of different subpopulations with various alterations in cellular functions and gene expression. A study would need to examine a very large number of older people, and it would need to look for patterns in gene expression that could help to group people into subpopulations and then identify the best predictive genes for each of those subpopulations.

Extension prompts:

2. "Genes foretell flu shot response" showed that analyzing how active certain genes are could predict how well a person would respond to the flu vaccine. Beyond what was mentioned in the article, what useful predictions could be made by analyzing gene activity?

Predicting in people, some animals or perhaps even plants: positive or negative immune system responses to other vaccines and various medications, susceptibility to various infectious diseases and non-infectious illnesses, previous exposure to various pathogens or chemical compounds, susceptibility of a tumor to various chemotherapeutic drugs or susceptibility of bacteria to various antibiotics, plus more.

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Cross-Curricular Discussion: Q

Directions: The following list of discussion questions is provided to help you take notes, brainstorm ideas and test your thinking in order to be more actively engaged in class discussions related to this article. All questions in this section are related to topics covered in "Genes foretell flu shot response."

BIOLOGICAL SCIENCES

Discussion questions:

1. What are genes and viruses made of and how do they replicate?

Extension prompts:

2. What do genes produce and how are their activity levels controlled?

3. How does the immune system specifically attack things that it recognizes should not be in your body?

4. How do vaccines work?

CHEMICAL SCIENCES

Discussion questions:

You may want to check out Cancer's Sweet Cloak Guide and explore Cross-curricular discussion: Q in the Chemical Sciences and Physical Sciences sections if you are interested in additional questions on protein composition and structure.

1. What is the difference between a physical change and a chemical change? Provide an example of each.

2. What are simple examples of physical changes and chemical changes for DNA?

Extension prompts:

3. Many vaccines contain an adjuvant. What is that?

4. Why might it be undesirable to have too little or too much of an adjuvant in a vaccine?

ENGINEERING AND EXPERIMENTAL DESIGN

Discussion questions:

1. Why is it harder for researchers to identify genes that could predict how well older people's immune systems respond to flu vaccines? How could a study deal with that problem?

Extension prompts:

2. "Genes foretell flu shot response" showed that analyzing how active certain genes are could predict how well a person would respond to the flu vaccine. Beyond what was mentioned in the article, what useful predictions could be made by analyzing gene activity?

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Activity Guide for Teachers: Catching the flu

Purpose: To gain a better understanding of influenza, its genomes, mutations and vaccines.

Procedural overview: This guided research activity encourages the exploration of public data and information to learn more about influenza's genes and proteins, how a flu vaccine is made and the nine human genes that predict how well a flu vaccine will work in a person.

Approximate class time: 40 to 60 minutes.

Materials:

- Activity Guide for Students: Catching the flu
- Internet access
- Recommended textbooks or other reference books

Notes to the teacher:
Depending on your preference, students can work through these questions either in class or at home, and either individually or in groups. Also, feel free to get creative with dividing up the questions or parts of questions among groups. For example, question 11 involved researching information about nine genes. This would be a good question to divide up among groups. It would allow students to present information to the rest of the class during a discussion.

The following websites and books are very good sources of information to provide your students:

- *Science News for Students*: "Explainer: What is a vaccine?" (https://www.sciencenewsforstudents.org/article/explainer-what-vaccine)
- *Science News for Students*: "Explainer: What is a virus?" (https://www.sciencenewsforstudents.org/article/explainer-what-virus)
- Uniprot Protein Data Base (http://www.uniprot.org)
- Protein Data Bank (http://www.rcsb.org/pdb/home/home.do)
- National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov)
- CDC Influenza (https://www.cdc.gov/flu/index.htm)
- ViralZone (http://viralzone.expasy.org)
- Virus Pathogen Resource (https://www.viprbrc.org)
- NCBI Influenza Virus Resource (https://www.ncbi.nlm.nih.gov/genomes/FLU/Database/nph-select.cgi?go=database)
- Lisa A. Urry, Michael L. Cain, Steven A. Wasserman, Peter V. Minorsky, and Jane B. Reece. 2016. *Campbell Biology*. 11th ed. Pearson. See especially Ch. 19 (Viruses) and Ch. 43 (Immune System).
- David M. Knipe and Peter M. Howley (eds.). 2013. *Fields Virology*. 6th ed. Lippincott Williams & Wilkins.
- Lauren Sompayrac. 2012. *How Pathogenic Viruses Think*. 2nd ed. Jones & Bartlett.
- Jane Flint, Vincent R. Racaniello, Glenn F. Rall, Anna Marie Skalka, and Lynn W. Enquist. 2015. *Principles of Virology*. 4th ed. 2 vols. American Society for Microbiology.

- John Carter and Venetia Saunders. 2013. *Virology: Principles and Applications*. 2nd ed. Wiley.
- Lauren Sompayrac. 2016. *How the Immune System Works*. 5th ed. Wiley Blackwell.
- Thao Doan, Roger Melvold, Susan Viselli, and Carl Waltenbaugh. 2013. *Lippincott's Illustrated Reviews: Immunology*. 2nd ed. Lippincott, Williams & Wilkins.
- Judith A. Owen, Jenni Punt, and Sharon A. Stranford. 2013. *Kuby Immunology*. 7th ed. Macmillan.
- Abul K. Abbas, Andrew H. Lichtman, and Shiv Pillai. 2017. *Cellular and Molecular Immunology*. 9th ed. Elsevier.
- Kenneth Murphy and Casey Weaver. 2016. *Janeway's Immunobiology*. 9th ed. Garland.
- William E. Paul (ed.). 2012. *Fundamental Immunology*. 7th ed. Lippincott Williams & Wilkins.

Student instructions and questions with answers:

Do research online or in books to answer the following questions. Write down your answers as you go and be prepared to discuss your findings in class.

1. Is the genome of a flu virus made of DNA or RNA, and is it single-stranded or double stranded?

Single-stranded RNA.

2. How many separate segments or pieces is the flu virus genome divided into? What genes are on each piece, what are the genes' associated proteins and what do those proteins do?

8 segments:

The PB2 genome segment yields the PB2 component of RNA polymerase.

The PB1 genome segment yields the PB1 component of RNA polymerase, PB1-F2 proteins that fight cellular defenses and PB1 N40 protein that's function is currently unknown.

The PA genome segment yields the PA component of RNA polymerase.

The HA genome segment yields HA hemagglutinin glycoproteins, which cover the surface of virus particles and help them enter and leave cells.

The NP genome segment yields NP proteins that are required for packaging of specific RNA segments.

The NA genome segment yields NA neuraminidase glycoproteins, which cover the surface of virus particles and help it enter and leave cells.

The M genome segment yields M1 matrix proteins, which help form the structure of virus particles, and M2 ion channels, which sense when the virus particles have gotten inside a cell.

The NS genome segment yields NS1 non-structural proteins that fight cellular defenses and NEP/NS2 non-structural proteins mediate export of viral ribonucleoprotein.

3. Different strains of influenza can have different versions of each of these genome segments. For the influenza A virus, how many known versions of HA are there?

There are at least 18 major variations, H1 through H18. There are also minor variations of each of these major variations to fool the immune system into thinking it has never seen the virus before.

4. For the influenza A virus, how many known versions of NA are there?

There are at least 11 major variations, N1 through N11. There are also minor variations of each of these major variations to fool the immune system into thinking it has never seen the virus before.

5. Including all of the known HA and NA versions, how many possible influenza A strains are there?

18 HA x 11 NA = 198 influenza A strains with different combinations of major variations of HA and NA on the surface of the virus. Including the minor variations, there are thousands or more of possible strains.

6. In terms of the benefits to the virus, why is it important for influenza to have so many possible HA and NA glycoprotein versions?

The surface of influenza virus particles are covered with HA and NA glycoproteins. If the virus particles change those glycoproteins, they can trick lymphocytes into thinking the immune system has never seen the flu virus before.

7. The annual flu vaccine usually contains HA and NA glycoproteins from three different flu strains. How many different strains could the vaccine protect against?

If a vaccine contains different HA and NA glycoproteins from three flu strains, there would be 3 possible HA types and 3 possible NA types, or 3 x 3 = 9 possible strains against which the vaccine could provide protection. That is a small fraction of the total number of possible flu strains that exist. The fraction is even smaller if you consider some of the three flu strains used to make the vaccine share an HA or NA type, or how many minor variations there can be in flu strains that could evade the vaccine.

8. Suppose that one flu virus strain has its own version of each of its genome segments, and a second flu virus strain has a different version of each of the genome segments. If both flu strains infect the same cell, the new virus particles that get assembled may end up with some genome segments from one strain and some from the other strain. Assuming that each new virus ends up with one copy of each genome segment, and that each genome segment can come from either original flu strain, how many possible flu strains could be produced by that one doubly-infected cell?

2 possibilities for each of 8 genome segments = 2^8 = 256 possible resulting strains

9. Why does the flu virus mutate so easily?

1. Reassortment of segments between different strains that infect the same cell, which is not a problem with viruses that only have one genome segment. 2. Errors produced by RNA polymerase in copying the genome; the viral RNA polymerase is much more error-prone than human DNA polymerase.

10. In what parts of the United States is the flu currently the worst? See: The Weekly US Map: Influenza Summary Update by the U.S. Centers for Disease Control and Prevention (https://www.cdc.gov/flu/weekly/usmap.htm)

Answers will vary over time.

11. Listed below are the nine genes whose activity was found to be correlated with strong immune responses to flu vaccines. From online searches, briefly summarize what is known about the function of each gene's corresponding protein, and speculate why the protein (and the amount of the protein produced, called its gene expression level) might be involved in strong immune responses to flu vaccines.

RAB24

Ras-related protein Rab-24. It is known to be involved in intracellular protein trafficking, like a postal worker helping the right envelopes get to the correct zip codes. Perhaps immune system cells or lymphocytes use this protein to help deliver components of antibodies and T cell receptors.

GRB2

Growth factor receptor-bound protein 2. Growth factor receptors help cells sense external signals that they should grow and divide. Perhaps the protein helps immune cells receive signals that they need to grow and multiply.

DPP3

Dipeptidyl-peptidase 3 serine protease. Serine proteases are involved in intracellular signaling. Perhaps the protein helps immune cells signal when they detect the vaccine.

ACTB

Beta-actin cytoskeleton. This protein is part of the skeleton that helps cells keep their proper shape and even move, just as your skeleton helps you keep your shape and move. Perhaps the protein helps immune cells maintain the best shape and move toward their targets.

MVP

Major vault protein. It is involved in helping to transport things in and out of the cell nucleus. Perhaps the protein helps immune system cells by helping signal other proteins to get into the nucleus or messenger RNAs to get out so that they can better respond to the vaccine.

DPP7

Dipeptidyl peptidase 7. It is involved in maintaining the resting state of immune system cells. Perhaps changes in its gene expression are involved in helping immune cells wake up and respond to the vaccine.

ARPC4

Actin related protein 2/3 complex subunit 4. It controls actin polymerization and is involved in controlling the shape and movement of the cytoskeleton. Perhaps the protein helps immune cells adjust their shape and movements to better respond to the vaccine.

PLEKHB2

Pleckstrin homology domain-containing family B member 2. It is involved in retrograde transport of recycled endosomes. Perhaps the protein helps in carrying B cell or T cell receptors that have detected vaccine components into the cell and initiating an immune response.

ARRB1

Arrestin beta 1. It is involved in dampening cellular responses to extracellular signals. Perhaps changes in its gene expression are involved in helping immune cells be more sensitive to vaccines.

12. What have you learned about influenza that has surprised you?

Student answers will vary.

SN EDUCATOR GUIDE

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Genes Foretell Flu Shot Response

Activity Guide for Students: Catching the flu

Purpose: To gain a better understanding of influenza, its genomes, mutations and vaccines.

Procedural overview: This guided research activity encourages the exploration of public data and information to learn more about influenza's genes and proteins, how a flu vaccine is made and the nine human genes that predict how well a flu vaccine will work in a person.

Resources:

- *Science News for Students*: "Explainer: What is a vaccine?" (https://www.sciencenewsforstudents.org/article/explainer-what-vaccine)
- *Science News for Students*: "Explainer: What is a virus?" (https://www.sciencenewsforstudents.org/article/explainer-what-virus)
- Uniprot Protein Data Base (http://www.uniprot.org)
- Protein Data Bank (http://www.rcsb.org/pdb/home/home.do)
- National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov)
- CDC Influenza (https://www.cdc.gov/flu/index.htm)
- ViralZone (http://viralzone.expasy.org)
- Virus Pathogen Resource (https://www.viprbrc.org)
- NCBI Influenza Virus Resource (https://www.ncbi.nlm.nih.gov/genomes/FLU/Database/nph-select.cgi?go=database)

Procedure:

Do research online or in books to answer the following questions. Write down your answers as you go and be prepared to discuss your findings in class.

1. Is the genome of a flu virus made of DNA or RNA, and is it single-stranded or double stranded?

2. How many separate segments or pieces is the flu virus genome divided into? What genes are on each piece, what are the genes' associated proteins and what do those proteins do?

3. Different strains of influenza can have different versions of each of these genome segments. For the influenza A virus, how many known versions of HA are there?

4. For the influenza A virus, how many known versions of NA are there?

5. Including all of the known HA and NA versions, how many possible influenza A strains are there?

6. In terms of the benefits to the virus, why is it important for influenza to have so many possible HA and NA glycoprotein versions?

7. The annual flu vaccine usually contains HA and NA glycoproteins from three different flu strains. How many different strains could the vaccine protect against?

8. Suppose that one flu virus strain has its own version of each of its genome segments, and a second flu virus strain has a different version of each of the genome segments. If both flu strains infect the same cell, the new virus particles that get assembled may end up with some genome segments from one strain and some from the other strain. Assuming that each new virus ends up with one copy of each genome segment, and that each genome segment can come from either original flu strain, how many possible flu strains could be produced by that one doubly-infected cell?

9. Why does the flu virus mutate so easily?

10. In what parts of the United States is the flu currently the worst? See: [The Weekly US Map: Influenza Summary Update](https://www.cdc.gov/flu/weekly/usmap.htm) by the Centers for Disease Control and Prevention (https://www.cdc.gov/flu/weekly/usmap.htm)

11. Listed below are the nine genes whose activity was found to be correlated with strong immune responses to flu vaccines. From online searches, briefly summarize what is known about the function of each gene's corresponding protein, and speculate why the protein (and the amount of the protein produced, called its gene expression level) might be involved in strong immune responses to flu vaccines.

RAB24

GRB2

DPP3

ACTB

MVP

DPP7

ARPC4

PLEKHB2

ARRB1

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Other Related Articles

Science News for Students: DIY Science: Snot Science Video and Blog Posts

Science News for Students: "Explainer: What is a vaccine?"
Readability score: 7.8

Science News for Students: "Explainer: What is a virus?"
Readability score: 7.0

Science News for Students: "New ways to fight the flu"
Readability score: 6.6

Science News for Students: "Getting a flu 'shot' could become as easy as sticking on a bandage"
Readability score: 6.8

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