ANNOTATION FORM

Source

#1

Area of Focus: Cystic Fibrosis and the likely cause of its popularity

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

MarkLubinsky, Author. *Hypothesis: Cystic Fibrosis Carrier Geography Reflects Interactions of Tuberculosis and Hypertension with Vitamin D Deficiency, Altitude and Temperature. Vitamin D Deficiency Effects and Cf Carrier Advantage*. Accessed 21 Sept. 2020.

8Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This source is a "short communication" titled *Hypothesis: Cystic fibrosis carrier geography reflects interactions of tuberculosis and hypertension with vitamin D deficiency, altitude and temperature. Vitamin D deficiency effects and cf carrier advantage.* It was posted on ScienceDirect.com.

Evidence

List 5 or more pieces of evidence that are of value from your research. Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 12), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period. Evidence can take a variety of forms. (e.g. numbers, facts, statistics, quotations)

1. CF carrier rates of 4% or more despite traditional homozygotic lethality suggest heterozygotic advantages," (Lubinsky par. 1)

2. "CF heterozygosity generally correlates with past areas of VDD" (Lubinsky par. 3).
3. "mutations can mitigate at least two deficiency sequelae: Tuberculosis susceptibility and hypertension" (Lubinsky par. 4).

4. "With this, European CF heterozygosity has been epidemiologically linked to a tuberculosis pandemic from the early 17th century on [1]" (Lubinsky par. 6).

5. "However, high carrier rates with altitude (Table 1) despite decreased tuberculosis [10], and intermediate heterozygosity without past pandemics, as in the Middle East [11], suggest additional factors. Hypertension is a good candidate: VDD increases blood pressure [12] and interacting obstetrical problems [13], while systemic blood pressure decreases with CF, possibly from increased sweat sodium loss [14], and carriers, especially women, had lower blood pressure [15]. Less inherited hypertension in whites than blacks [16], [17] is also consistent with selection against high blood pressure in areas of past VDD" (Lubinsky par. 7).

6. "ΔF508, the most common CF allele [2], may be especially selected for here, following cooler temperatures with an increasing Southeast to Northwest European frequency [2], [21], as well as altitude (Table 1, and possibly Baluchistan [3]). Supporting a link to hypertension, other salt regulating genes also correlate with latitude, and with altitude, as with Basques [22], [23]. Contrariwise, relatively low ΔF508 rates in Ashkenazi Jews [2] are consistent with a greater role for selection against tuberculosis in this group [24]" (Lubinsky par. 9).

7. "Together, these factors help explain most of the geography of CF carriers:

1. Protection from tropical factors such as typhoid fever can favor certain metabolically neutral CFTR polymorphisms [25], [26]. However, heterozygous CF alleles can cause salt losses [27], and, even when similarly protective, were eliminated in these areas by a need for retention in the face of heat losses [15].

2.Outside of the tropics, VDD from decreased light selected for greater Vitamin D production *and* for amelioration of VDD effects, while selection for salt retention was relaxed or reversed [15].

3.Hypertension associated with VDD and with salt retention in non-tropical areas

selected for CF and other mitigating genes affecting sodium metabolism.

4.Worsening of VDD and hypertension with cold resulted in a CF temperature/latitude gradient.

5.While VDD could decrease with altitude, blood pressure remained an important selective force at high elevations because of greater hypertensive mortality with cold and/or altitude.

6.VDD related susceptibility to tuberculosis helped define the scope and timing of a European pandemic that began in the 17th century.

7.Tuberculosis subsequently selected for CF carrier protection in that same area.

8.Different CF alleles may have different protective effects: ΔF508 associates with areas of hypertensive risk, while others are more linked to tuberculosis. Alleles effective against typhoid, cholera, and other factors [26] may also have had a role in certain non-tropical areas" (Lubinsky par. 10).

Summarize

- For each source, write a thoughtful, well-structured paragraph. **Synthesize** (combine into a coherent whole) the information in the source. Consider including the thesis, main argument, and point of view, author's purpose, and what topics are covered.

- Include at least 3 quotes from the source with in-text citations to support your writing. Choose well so that you can refer back to these valuable quotations in your future work.

Organizing your findings into a concise piece of writing for each of your research assignments will help solidify your understanding of what you read and help you to actively evaluate and assess its importance to your topic. This documentation will also be used as support for presentations in class, interviews of experts in the field, and ultimately for your Lit Review Presentation. The more detailed you can be here the better for your future work.

This hypothesis expanded the answer to why the mutation delta F508 is so prevalent in some areas. It argues that there is more of an explanation than just one epidemic like typhoid fever in Europe circa 430BC and the 1940s. It argues that "CF carrier rates of 4%

or more despite traditional homozygotic lethality suggest heterozygotic advantages" (Lubinsky par. 1). With this, it gives explanations to why this heterozygotic advantage is appearing. The first main idea is that "VDD related susceptibility to tuberculosis helped define the scope and timing of a European pandemic that began in the 17th century"(Lubinsky par. 10). This article credits VDD, vitamin D deficiency, to the tuberculosis pandemic in Europe in the 17th century. This pandemic has been linked to being a cause of the CFTR protein mutation delta F508, the most common form of Cystic fibrosis. The second main idea is that "Different CF alleles may have different protective effects: ΔF508 associates with areas of hypertensive risk, while others are more linked to tuberculosis. Alleles effective against typhoid, cholera, and other factors [26] may also have had a role in certain non-tropical areas" (Lubinsky par. 10). The idea states that it can not be pinned to one cause, rather than multiple in multiple locations leading to multiple forms of CF.

Assess and Reflect

In a thoughtful, well-structured 3-5 sentence paragraph, **evaluate** the source. (How is it useful? Is it reliable, biased, objective? What is its goal? Does it meet it?) And then **reflect** on the source's specific value for your research. (How the source fits into your research. Does it help to shape your argument? How does it compare to other sources you've read? How will you use it? Has it changed your thinking?)

This could also be a place to include questions the research raises for you and/or connections you have made.

This hypothesis is a very credible source. Whenever it claims a controversial statement it cites the evidence supporting it. There are many scholarly articles cited. This article appears not too biased. Of course, with any piece of writing that includes a claim, there is a bias. This hypothesis has shaped my topic down a road specifically of CF. I think that this narrowing will help me later when I have to present on one topic. It also showed me that there is so much more to learn. I will use this as a start to my research going down all the roads of possible causes mentioned.

ANNOTATION RUBRIC

Source

#3

Area of Focus CF Heterozygote advantage

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

Högenauer, Christoph. "Active Intestinal Chloride Secretion in Human Carriers of Cystic Fibrosis Mutations: An Evaluation of the Hypothesis That Heterozygotes Have Subnormal Active Intestinal Chloride Secretion." *PubMed Central (PMC)*, 1 Dec. 2000, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1287919/.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This is a published medical hypothesis. It is on the website of the National Center for Biotechnology Information.

Evidence

List 5 or more pieces of evidence that are of value from your research. Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 12), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period. Evidence can take a variety of forms. (e.g. numbers, facts, statistics, quotations)

1. "Approximately 1 in 3,000 white babies is born with the disease" (Högenauer par. 1)
2. "28 healthy white adults is a carrier of a CF gene mutation" (Högenauer par. 1).
3. "CFTR mediates secretory diarrhea due to the toxins of *Vibrio cholerae* and *Escherichia coli,* it was logical to propose that the high frequency of CF mutations in the white population may be due to protection of heterozygotes from dehydration due to diarrheal diseases" (Högenauer par. 2).
4. "mice that were heterozygous for CF were shown to have one half the normal amount of CFTR protein and one half the normal intestinal fluid secretion after exposure to cholera toxin" (Högenauer par. 3).
5. "CF mutations are not common in areas of the world where infectious diarrhea is most common and most lethal" (Högenauer par. 4).
6. "The rate-limiting step at the heterozygote level of CFTR expression could be one of three factors: (1) the degree to which intracellular cyclic nucleotides are increased by a secretagogue; (2) the response of transporters on the basolateral membrane of epithelial cells, which are involved in establishing the

electrochemical gradients that cause chloride to exit epithelial cells through the CFTR channels (Field and Semrad 1993); or (3) the release of neurotransmitters that are apparently essential for secretagogue action (Lundgren et al. 1989; Castagliuolo et al. 1994)" (Högenauer par. 15).

7. "Our results provide evidence against the theory that CF heterozygotes have a survival advantage when they contract diarrhea mediated by stimulation of active intestinal chloride secretion. Our results are obviously not applicable to protection of CF heterozygotes against other pathogenetic factors involved in the production of diarrhea" (Högenauer par20).

Summarize

- For each source, write a thoughtful, well-structured paragraph. **Synthesize** (combine into a coherent whole) the information in the source. Consider including the thesis, main argument, and point of view, author's purpose, and what topics are covered.

- Include at least 3 quotes from the source with in-text citations to support your writing. Choose well so that you can refer back to these valuable quotations in your future work.

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This article covers the hypothesis that CF heterozygotes have a higher evolutionary fitness than normal people. They start off examining both sides of the argument and state evidence of both sides. They discuss that "CF mutations are not common in areas of the world where infectious diarrhea is most common and most lethal" (Högenauer par. 4). This is against the assumption that being a CF heterozygote allows you to secrete less out of the CFTR protein causing a high evolutionary fitness. They do note that "mice that were heterozygous for CF were shown to have one half the normal amount of CFTR protein and one half the normal intestinal fluid secretion after exposure to cholera toxin" (Högenauer par. 3). The Hypothesis is that CF heterozygotes secrete less intestinal Chloride than normal people when exposed to toxins and diarrheal infections and because of this they are more likely to reproduce. They tested the amount of intestinal chloride secretion in people with CF, CF heterozygotes, and normal for the CF mutation. They only tested the delta f508 mutation because it is the oldest and most common and makes the most sense to be the mutation responsible. Their results concluded that "CF heterozygotes have a survival advantage when they contract diarrhea mediated by

stimulation of active intestinal chloride secretion" (Högenauer par20). They noted that this does not explain the popularity of CF.

Assess and Reflect

In a thoughtful, well-structured 3-5 sentence paragraph, **evaluate** the source. (How is it useful? Is it reliable, biased, objective? What is its goal? Does it meet it?) And then **reflect** on the source's specific value for your research. (How the source fits into your research. Does it help to shape your argument? How does it compare to other sources you've read? How will you use it? Has it changed your thinking?)

This could also be a place to include questions the research raises for you and/or connections you have made.

This source proved to be useful for my topic. It addressed CF heterozygotic advantages and scientific accuracy. It was unbiased and acknowledged both sides of the argument and was simply informational. Its goal is to analyze the question of the popularity of CF. This source goes against what I originally thought about heterozygotic advantages. This source leaves me with more questions than answers. I might do a deeper down heterozygotic advantage.

ANNOTATION FORM

Source

#2

Area of Focus: Cystic Fibrosis Treatments

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

"CFTR Modulator Therapies." *Cystic Fibrosis Foundation*, https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/. Accessed 30 Sept. 2020.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This is an informational website page on the Cystic Fibrosis Foundation (CFF) website.

Evidence

List 5 or more pieces of evidence that are of value from your research. Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 12), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period. Evidence can take a variety of forms. (e.g. numbers, facts, statistics, quotations)

1. "There are four CFTR modulators for people with certain CFTR mutations: ivacaftor (Kalydeco®) lumacaftor/ivacaftor (Orkambi®) tezacaftor/ivacaftor (Symdeko®) elexacaftor/tezacaftor/ivacaftor (Trikafta™)" (CFF par. 1).
2. "The CFTR protein regulates the proper flow of water and chloride in and out of cells lining the lungs and other organs" (CFF par. 3).
3. "Like lumacaftor and tezacaftor, elexacaftor also helps the F508del-CFTR protein form the right shape so that it can traffic to the cell surface...helps the CFTR protein perform better than other modulators for an even greater number of people with CF" (CFF par. 6).
4. "Ivacaftor, a CFTR modulator known as a potentiator, binds to the defective protein at the cell surface and opens the chloride channel (holds the gate open) so that chloride can flow through, regulating the amount of fluids at the surface of the cell" (CFF Par. 7).
5. "Lumacaftor is a modulator known as a corrector. It helps the F508del-CFTR protein form the right shape, traffic to the cell surface, and stay there longer. But, even with lumacaftor, only about a third of the CFTR protein reaches the cell surface, and those proteins do not open enough to allow chloride to pass through the cell membrane. If a corrector is used in combination with a potentiator -- such as ivacaftor -- to hold the gate on the CFTR protein open, enough chloride can then flow to reduce the symptoms of CF" (CFF par. 9).
6. "tezacaftor/ivacaftor combination has been shown to have fewer side effects -- such as chest tightness -- and drug interactions than lumacaftor/ivacaftor" (CFF par. 11).
7. "The effects of CFTR modulators only last for as long as the medication is in your system" (CFF par. 14).

Summarize

- For each source, write a thoughtful, well-structured paragraph. **Synthesize** (combine into a coherent whole) the information in the source. Consider including the thesis, main argument, and point of view, author's purpose, and what topics are covered.

- Include at least 3 quotes from the source with in-text citations to support your writing. Choose well so that you can refer back to these valuable quotations in your future work.

Organizing your findings into a concise piece of writing for each of your research assignments will help solidify your understanding of what you read and help you to actively evaluate and assess its importance to your topic. This documentation will also be used as support for presentations in class, interviews of experts in the field, and ultimately for your Lit Review Presentation. The more detailed you can be here the better for your future work.

This website page discusses the various CFTR, Cystic fibrosis transmembrane conductance regulator, modulators that are used in treatment. A CFTR protein, "regulates the proper flow of water and chloride in and out of cells lining the lungs and other organs" (CFF par. 3). These modulators help improve this protein's function despite its mutation. There are four modulators that have been synthesised and are used in treatment: "ivacaftor (Kalydeco®) lumacaftor/ivacaftor (Orkambi®) tezacaftor/ivacaftor (Symdeko®) elexacaftor/tezacaftor/ivacaftor (Trikafta™)" (CFF par. 1). The Cystic Fibrosis Foundation website discusses the pros and cons of each CFTR modulator. The best CFTR modulator was Trikafta because it offered a three in one combo of modulators. Each Modulator corresponds with different mutations. Some work better than others in some people but are useless in others. These modulators are not cures. They are treatments and only last as long as the drugs do. Once your body processes them out of your system you need to take more again (CFF par. 14).

Assess and Reflect

In a thoughtful, well-structured 3-5 sentence paragraph, **evaluate** the source. (How is it useful? Is it reliable, biased, objective? What is its goal? Does it meet it?) And then **reflect** on the source's specific value for your research. (How the source fits into your research. Does it help to shape your argument? How does it compare to other sources you've read? How will you use it? Has it changed your thinking?)

This could also be a place to include questions the research raises for you and/or connections you have made.

This source is useful to me. It is an unbiased, factual website page. Its objective is to educate the public and specifically CF patients about CFTR modulators. It accomplishes its goal. This source showed me other drugs than just Trikefta. It also will help me explain my topic, and help my views understand what I am talking about. This source has pushed me down a treatment path that I might follow for a while.

Annotation Notes Form

Source

#4

Area of Focus CF Treatment

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

"CFTR - Johns Hopkins Cystic Fibrosis Center." *Johns Hopkins Cystic Fibrosis Center*, https://hopkinscf.org/knowledge/cftr/. Accessed 10 Dec. 2020.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

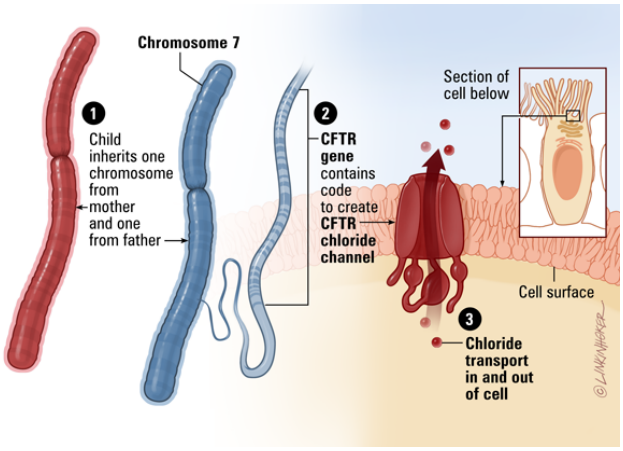
This is an informational website page on John Hopkins CF Center website about CFTR proteins and CF.

Notes

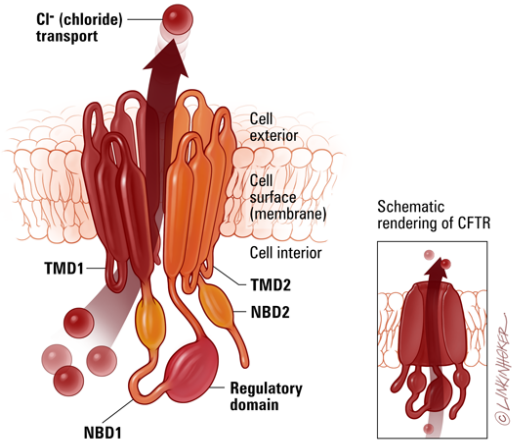
Use this box as a place to list information from the source that is of value to your research along with ideas and understandings the source brought about for you. Just as when you annotate a book for a class, here you'll include information like what you would highlight, margin notes, questions, quotations, connection to other sources, and evidence in the form of data representations (charts/graphs). Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 9), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period.

As you have done with your annotations, consider including the thesis, main argument and how this source or information fits into your research.

1. The CFTR protein can be found in 7 different organs (Johns Hopkins Cystic Fibrosis Center par. 3).
2. CFTR proteins transport chloride and other molecules (Johns Hopkins Cystic Fibrosis Center par. 1).
3. "Since the discovery of the *CFTR* gene in 1989, more than 2,500 mutations have been identified" (Johns Hopkins Cystic Fibrosis Center par. 1).
4. It is located on chromosome 7 (Johns Hopkins Cystic Fibrosis Center par. 1).

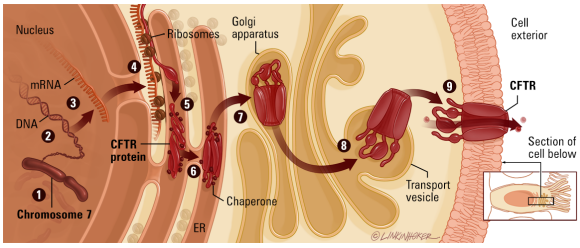


5. (Johns Hopkins Cystic Fibrosis Center figure: 1)
6. There are 1480 amino acids in the CFTR protein (Johns Hopkins Cystic Fibrosis Center par. 2).
7. ". Mutations in CFTR often affect the three-dimensional structure of the protein and prevent CFTR from reaching the membrane" (Johns Hopkins Cystic Fibrosis Center par. 2).



8. (Johns Hopkins Cystic Fibrosis Center figure: 2)
9. CF patients have a high salt rate in their sweat. The lack of CFTR function leads to this (Johns Hopkins Cystic Fibrosis Center par. 4).
10. The mucus layer in CF patient's lung become dehydrated due to defective CFTR

proteins and build up thicker than a normal person (Johns Hopkins Cystic Fibrosis Center par. 5.

11. CF patients do not make pancreatic enzymes or bicarbonate. Cf patient's inability to neutralize stomach acid contributes to malabsorption (Johns Hopkins Cystic Fibrosis Center par. 6).
12. "Located on the long (q) arm of chromosome 7 at position 31.2, the *CFTR* gene is comprised of 27 exons that encode its genetic sequence (1). An exon is a portion of a DNA that contains the code for a protein structure. The *CFTR* gene is transcribed into a single strand of RNA within the cell nucleus (2); regions that are not needed to make the protein are spliced out, producing the final messenger RNA (mRNA) (3). The mRNA leaves the nucleus (4) and is translated into protein by ribosomes in the endoplasmic reticulum, or ER (5). A number of proteins called chaperones (6), facilitate folding of the new CFTR protein and its to the Golgi apparatus (7) where sugars are added. The CFTR protein then travels (8) to cell surface (9)" (Johns Hopkins Cystic Fibrosis Center par. 7).
13. 

(Johns Hopkins Cystic Fibrosis Center figure: 4)

Class 1 mutations

No CFTR protein is produced. Class 1 mutations can be due to early termination of CFTR protein production or large regions of mutated CFTR DNA.

Class 2 mutations

Defective trafficking of CFTR, which does not reach the surface of the cell. F508del is a class 2 mutation.

Class 3 mutations

The CFTR protein reaches the cell surface but it does not function. G551D is a class 3 mutation.

Class 4 mutations

The CFTR protein reaches the cell surface but chloride transport through the channel is defective.

Class 5 mutations

The CFTR channel is normal but the amount of protein at the cell surface is decreased.

Class 6 mutations

The CFTR channel is not stable at the cell surface so the amount of protein at the cell surface is decreased.

14. (Johns Hopkins Cystic Fibrosis Center par. 8)
15. This will benefit my presentation and explanation of what CF is.

Annotation Notes Form

Source

#5

Area of Focus Treatment: Gene editing

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

"Gene Editing for Cystic Fibrosis." *Cystic Fibrosis Foundation*, https://www.cff.org/Research/Research-Into-the-Disease/Restore-CFTR-Function/Gene-Editing-for-Cystic-Fibrosis/. Accessed 22 Oct. 2020.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This source is a website page on the CF Foundation's website titled "Gene Editing for Cystic Fibrosis".

Notes

Use this box as a place to list information from the source that is of value to your research along with ideas and understandings the source brought about for you. Just as when you annotate a book for a class, here you'll include information like what you would highlight, margin notes, questions, quotations, connection to other sources, and evidence in the form of data representations (charts/graphs). Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 9), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period.

As you have done with your annotations, consider including the thesis, main argument, and how this source or information fits into your research.

1. CF is an autosomal recessive disease. (Cystic Fibrosis Foundation par. 1)
2. Gene editing uses the cell's own tactics of correcting DNA (Cystic Fibrosis Foundation par. 1).
3. The tricky part of gene editing is getting that machinery inside the cell to perform its task (Cystic Fibrosis Foundation par. 2).
4. Once inside the cell nucleus 20 letters out of the 3 billion need to be identified and corrected for the edit to fix the CFTR protein being encoded (Cystic Fibrosis Foundation par. 3).
5. CRISPR is the most-used gene-editing tool. It is cheap and easy to set to which part of the DNA you want to correct (Cystic Fibrosis Foundation par. 4)
6. "Once the tools enter the cell and reach the mutated sequence of DNA, the scissors snip out the mutation. This damage attracts the attention of the cell's DNA repair machinery, which will then use the template to fix the break in the DNA" (Cystic Fibrosis Foundation par. 6).
7. Editing a gene permanently fixes the gene and all future cells produced to keep the

new edit (Cystic Fibrosis Foundation par. 6).

8. "There are other tools that can be used for gene editing, including proteins called TALENs, meganucleases, and zinc finger nucleases. These all work in a similar way to CRISPR, but they are less popular because they are harder to customize and require a lot more time and expertise from researchers" (Cystic Fibrosis Foundation par. 7).
9. There are more than 1700 CF mutations making gene editing tricky (Cystic Fibrosis Foundation par. 9).
10. "Sometimes, gene-editing tools break the DNA in the wrong place in the genome" (Cystic Fibrosis Foundation par. 10).
11. Errors can result in a higher risk of cancer (Cystic Fibrosis Foundation par. 10).
12. "the cell's DNA repair machinery can only complete its work if the cell undergoes a round of cell division" (Cystic Fibrosis Foundation par. 11).
13. Lung cells do not divide which means the stem cell of the lung cells might have to be specifically targeted to fight CF (Cystic Fibrosis Foundation par. 11).
14. This source is credible
15. It is pushing me to research treatment more, specifically gene editing.

ANNOTATION FORM

Source

#6

Area of Focus_Heterozygote Advantage

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

"Heterozygote Advantage - an Overview | ScienceDirect Topics." *ScienceDirect TopicsScienceDirect*, https://www.sciencedirect.com/topics/medicine-and-dentistry/heterozygote-advantage. Accessed 29 Oct. 2020.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This is a website page of a collection of different pieces of work from different books regarding Heterozygote Advantage.

Evidence

List 5 or more pieces of evidence that are of value from your research. Each piece of evidence needs to be followed by an in-text citation. If there are distinct page numbers in the source include those (Roy 12), if not, use the paragraph number (Roy par. 13). Indicate what the timestamp is on podcasts and videos (Roy 2:12). The citation comes right before the period. Evidence can take a variety of forms. (e.g. numbers, facts, statistics, quotations)

1. Heterozygote advantage develops when the fitness of a heterozygote is greater than that of a homozygote (R.S. Singh, R.J. Kulathinal par. 1).
2. Sickle cell disease has a heterozygote advantage against malaria and those with one sickle cell allele are more fit (R.S. Singh, R.J. Kulathinal. 1).
3. "heterozygote advantage is both necessary and sufficient to ensure that any population with allele frequencies close to those at this equilibrium will evolve toward that equilibrium" (H.G. Spencer par. 1).
4. "It turns out that heterozygote advantage is neither necessary nor sufficient to maintain all the alleles at a stable equilibrium" (H.G. Spencer par. 2).
5. Proof of the CFTR delta F508 gene mutation having a heterozygote advantage has been, "somewhat elusive" (Michael F. Murray par. 1).

Summarize

- For each source, write a thoughtful, well-structured paragraph. **Synthesize** (combine into a coherent whole) the information in the source. Consider including the thesis, main argument, and point of view, author's purpose, and what topics are covered.

- Include at least 3 quotes from the source with in-text citations to support your writing. Choose well so that you can refer back to these valuable quotations in your future work.

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This source is a combination of multiple sources that speak upon heterozygote advantage. It provides context to what heterozygote advantage is in other situations. It discussed the mathematical science behind it. Heterozygote advantage develops when the fitness of a heterozygote is greater than that of a dominant and recessive homozygote (R.S. Singh, R.J. Kulathinal par. 1). Sickle cell disease has a heterozygote advantage against malaria and those with one sickle cell allele are more fit (R.S. Singh, R.J. Kulathinal. 1). This is clear and has been proven by multiple people. Proof of the CFTR delta F508 gene mutation having a heterozygote advantage has been "somewhat elusive" (Michael F. Murray par. 1). This source says that the proof for a heterozygote advantage of Cystic Fibrosis has not been found yet. It defines what heterozygote advantage is and gives equations and graphs to calculate the genetic variation in populations.

Assess and Reflect

In a thoughtful, well-structured 3-5 sentence paragraph, **evaluate** the source. (How is it useful? Is it reliable, biased, objective? What is its goal? Does it meet it?) And then **reflect** on the source's specific value for your research. (How the source fits into your research. Does it help to shape your argument? How does it compare to other sources you've read? How will you use it? Has it changed your thinking?)

This could also be a place to include questions the research raises for you and/or connections you have made.

This source proved to be useful. It is unbiased and collects data from multiple sources. Its goal is to offer different approaches to help define and explain heterozygote advantage. This source really pushed me to want to give my answer to the heterozygote advantage question regarding CF. There isn't any answer out there and I want to be able to answer it.

Annotation Notes Form

Source

#7

Area of Focus_Treatment: Gene Editing_

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

A.Hodges, Craig. *Delivering on the Promise of Gene Editing for Cystic Fibrosis*. https://www.sciencedirect.com/science/article/pii/S2352304218301363. Accessed 11 Mar. 2020.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

This source is a published article posted on the website ScienceDirect.

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As you have done with your annotations, consider including the thesis, main argument, and how this source or information fits into your research.

1. "Cystic fibrosis causes severe impairment of lung function, serious pathology of the pancreas and gut, male infertility and reduced growth" (Hodges par. 1). This gives a basic description of the symptoms of Cystic Fibrosis and will be beneficial to my presentation.
2. The other mutations than delta F508 are random mutations like deletions, slices, and duplicates (Hodges par. 3).
3. Cas9 is 1368 amino acids long and binds to a guide RNA (Hodges par. 15).
4. Cas9 is responsible for cutting DNA in a sequence that then can later be worked with (Hodges par. 15).
5. "F508del mutation constrains strategies to correct it--as pointed out, base editors cannot correct this mutation" (Hodges par. 37). This means that other forms of mutations can be corrected and not lead to CF, but this one can not be fixed by the body.
6. Many trials have focused on editing insertions and deletions. This helps focus on many alleles of the same gene. (Hodges par. 40).
7. "A single, targeted insertion strategy could be applied to many different CF disease alleles.69 The goal is to insert coding sequences into an intron in the CFTR gene.70 The inserted DNA would have a splice acceptor and a continuous

open reading frame for the downstream exons. The earlier the intron in the gene, the greater the number of different alleles which could be corrected by this strategy" (Hodges par. 41). This means that an allele would permanently be fixed and that all the other alleles generated from this one would have its fixed DNA. The earlier this is done the greater the effect down the road.

8. "The majority of disease-causing variants are loss-of-function mutations" (Hodges par. 45). This shows that deletion corrections by editing are not really useful unless targeting a specific allele.
9. "There are specific CFTR alleles with intronic mutations that lead to disruption of splicing. Deletion of these mutations has led to the restoration of CFTR splicing and function in vitro.76 However, of the common mutations which affect CFTR splicing (Table 1), two are 1 base pair from an intron-exon junction (Fig. 1) and thus are not candidates for correction by deletion" (Hodges par. 48). This means that CF is out of the equation for a deletion correction to fix its alleles.
10. There is an idea of reducing the epithelial sodium channel function to help fix the ion balance airway epithelium and ameliorate disease pathology (Hodges par. 49).
11. "The three base pair deletion and transversions currently can be precisely repaired with Cas9 by generating a double-strand break and utilizing HDR" (Hodges par. 50). This means that the most common CF mutation Delta F508 can be repaired.
12. In order to perform an all at once treatment for CF a "sufficient number of stem cells" would have to be treated at once (Hodges par. 51).
13. "In the lifetime of a treated patient, it is reasonable to assume that, between normal turnover and injuries due to infection or physical insult, replacement and regeneration of apical epithelial cells from basal stem cells will occur. Thus, for long term functional restoration from a single treatment, gene editing needs to be targeted to the basal stem cells" (Hodges par. 52). This describes how and where a one-time treatment would take place and how it would work in the lungs which used to be thought to never regenerate cells.

Annotation Notes Form

Source

#8

Area of Focus_ Neurological Side Effects of CF_

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

Ellis, Samantha. "CNS Imaging Studies in Cystic Fibrosis Patients Presenting with Sudden Neurological Events." *PubMed Central (PMC)*, 1 Jan. 2019, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6688669/.

Description

What type of source is it? (e.g. book, article, website, blog, interview, video)

A scientific article uploaded to a website.

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1. This source covers the effects Cystic Fibrosis has on the Central Nervous System (Samantha par. 1).
2. 476 medical cases of CF patients from 2000 to 2018 of patients who experienced acute neurological events received MRIs and were studied (Samantha par. 2).
3. "Acute neurological presentations, excluding headaches without associated neurological symptoms, were reported in 27 index patients out of the 476 patients" (Samantha par. 3).
4. The most common trait among these patients were seizures and transient motor or sensory deficit (Samantha par. 3).
5. "The majority of these events were transient episodes (Samantha par. 12)."
6. There were no events that could make sense of the unknown causes (Samantha par. 13).

7. “lesions thought to be consistent with ischemia were seen in the hippocampus, occipital cortex, posterior thalamus, and parietal cortex”(Samantha par. 14).
8. These have been seen in healthy CF adults (Samantha par. 13).
9. CFTR has been found in brain tissue (Samantha par. 14).
10. “In humans, this appears to be only within neuronal cells, and not in astrocytes or radial glial cells” (Samantha par. 14).
11. “The CFTR protein is involved in various functions, including neuronal development38 and neuronal cell apoptosis, with reduced neuronal CFTR protein function associated with mitochondrial oxidative stress” (Samantha par. 14).
12. This means that CF does have a neurological effect on people with CF but to what magnitude and popularity are still unknown. This is leading me to research further into this topic.

Annotation Notes Form

Source

#9

Area of Focus_Psychiatric side of CF__

Provide the Bibliographic Citation for your source including the URL or DOI if available. (This is the quick way to link back to the source.)

P.E.PfefferJ.M.PfefferM.E.Hodson, Author. *The Psychosocial and Psychiatric Side of Cystic Fibrosis in Adolescents and Adults*. https://www.sciencedirect.com/science/article/pii/S1569199303000201. Accessed 12 Sept. 2020.

Description

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1. "tested adults with cystic fibrosis and found a prevalence of anxiety of 22.2% and depression of 42.4% (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 3).
2. CF patients are less likely than a control group to be employed (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 4).
3. "However, CF does have a negative impact on physical functioning aspects of quality of life. Nevertheless, a large proportion of adults with CF are living full and productive lives [8]." (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 4).
4. "that male gender was, if anything, a predictor of psychiatric emotional disturbance (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 8)."
5. They believe that men are affected more because of Anglo-Saxon culture and western culture believing Men should be the provider (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 9).
6. "quality of life in older men increasingly worse than scores in a healthy population of the same age (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 10)."
7. Women did not show a similar trend (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 10).
8. I do not know of any trans or gender fluid CF patients, but I wonder how they would react and if it would fit with the statistics based on their sex.
9. "Female adolescents rely heavily on denial" for coping(P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 11).
10. The men were found to rely on behavioral problems and were found to stay in the hospital less than women even with the same amount of health issues. (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 11)."
11. This all aligns with society's harder pressure on men to be healthy both physically and mentally causing them to bring their disease into their "self-concept" (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 11)."
12. "the social pressure of women being slim may encourage poor nutrition in female patients" (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 12).

13. Although these pressures might affect their mental state there is not trend between life expectancy and sex regarding CF patients. (P.E.Pfeffer, J.M.Pfeffer, M.E.Hodson par. 12).