NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

# DeafBlind Cajuns*

*by*
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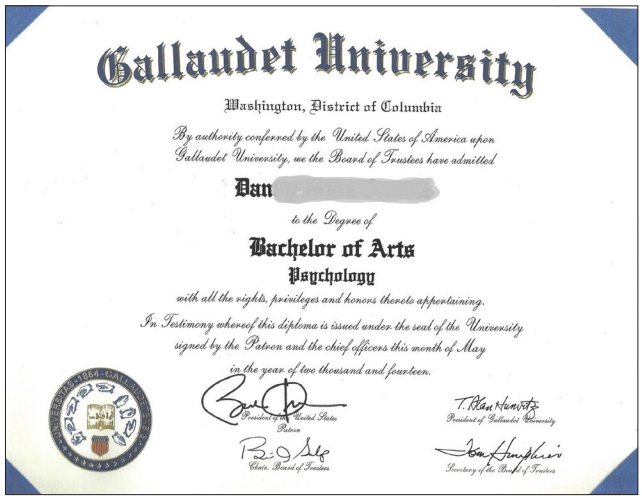
## Part I – Meet Dan and Annie

Annie pulled a chair for me at their dining room table and brought out snacks while her husband Dan made his way from the back of the house with his new diploma. Dan did not need to use his white cane inside their home. Since I am not fluent in American Sign Language (ASL), Annie offered me a blank, boldly lined tablet labeled "low-vision notebook" and a thick black marker. I wrote "Congratulations!" when Dan proudly showed me his diploma from Gallaudet University (Figure 2), the only deaf-serving university in the world. He recently completed a BA degree in psychology and now is back home in Louisiana working as a case manager for deaf and deafblind residents at a local nursing home (Figure 3). Since Dan's vision has deteriorated more than Annie's, she used a tactile form of American Sign Language (tactile ASL) to convey what I wrote by signing into Dan's hands.

*Figure 1.* Dan and Annie.

Dan and Annie are deafblind. They were born profoundly deaf and began to lose their peripheral and night vision in their late teens. Dan, now in his 50s, has only a small part of his central vision left. He uses adaptive technologies that magnify printed text and a white cane for mobility. Annie, who is in her 40s, has not lost as much of her peripheral vision yet, but navigating in low light, such as in dark restaurants, is becoming more difficult. Both have received immersive training in Braille and independent living strategies in



Gallaudet University

Washington, District of Columbia

By authority conferred by the United States of America upon Gallaudet University, we the Board of Trustees have admitted

Dan [redacted]

to the Degree of

Bachelor of Arts

Psychology

with all the rights, privileges and honors thereto appertaining.

In Testimony whereof this diploma is issued under the seal of the University signed by the Patron and the chief officers this month of May in the year of two thousand and fourteen.

*Figure 2.* Dan's diploma.

*Figure 3.* Dan communicates with a deafblind resident of the nursing home using tactile ASL.

*Throughout this case study the varying use of uppercase and lowercase is intentional. "Deaf" and "DeafBlind" are capitalized when referring to the culture and community, whereas "deaf" and "deafblind" are not capitalized when referring to the medical or biological condition. The hyphenated format "deaf-blind" is older but is still occasionally used.

preparation for their declining vision. They stopped driving in their thirties and still live independently in their own home. They qualify for assistance with driving, shopping, and doctors' appointments by specially trained support service providers who are fluent in tactile ASL. By retirement age, their vision will be limited to the very center of their visual field. Using high-contrast screens, special light conditions and magnifiers will allow them to use their remaining vision to read as long as possible before relying only on Braille.

Although some deafblindness, like Helen Keller's, is due to illness in pregnancy or infancy, Dan's and Annie's deafblindness is due to a gene variant that came to Louisiana with the Acadians who settled the region in the 1700s. 10–20% of deaf people in Louisiana eventually lose their vision.

Genetic forms of deafness accompanied by retinal deterioration (retinitis pigmentosa or RP) and vestibular (balance) problems are called Usher syndrome. The genes that cause Usher syndrome are pleiotropic since a mutation in a single gene affects more than one phenotype. All forms of Usher syndrome around the world are categorized into three types based on severity and onset of symptoms. The phenotypes of Type 1 are profound deafness at birth, delayed walking and progressive RP beginning in adolescence. Dan and Annie have Type 1C, also called Acadian Usher syndrome.

Cajuns are the descendants of Acadians and other French-speaking settlers in southern Louisiana. Dan and Annie are leaders in the Cajun Deaf/DeafBlind community in Lafayette, Louisiana where many Acadians settled. They host a monthly chat at a local coffee shop that is attended by many Deaf and DeafBlind Cajuns and others who enjoy conversing in ASL (Figure 4).

Dan and Annie are real. They gave permission to use their names, stories and photos for this case study.

*Figure 4.* Monthly Deaf/DeafBlind social at local coffee shop

## Part II – Eyes and Ears

The *USH1C* gene encodes harmonin, a cytoskeletal protein expressed in the hair cells of the cochlea and semicircular canals, and the photoreceptors of the retina. Harmonin is one of many proteins found in the stereocilia that extend from the hair cells. Because of its central role as a scaffolding protein for other proteins, the result is severe malformation of the stereocilia and therefore profound deafness. Neither Dan nor Annie has ever heard a sound.

In the retinal photoreceptors, harmonin has been found concentrated in the narrow neck between the cell body and outer segment. Its exact function there is not known, but it is necessary for photoreceptor maintenance and health. The death of photoreceptors over time, from the periphery of the retina to the center, leads to dark splotches (Figures 5a and b) and tunnel vision that are characteristic of RP. A retinal specialist diagnoses and monitors RP with eye exams.

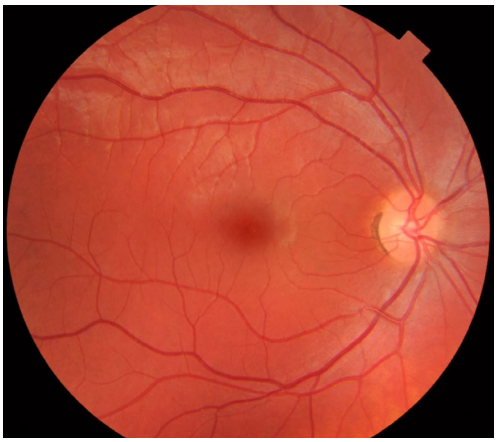


*Figure 5a*. Fundus of normal retina. *Credit:* Mikael Häggström, PD.

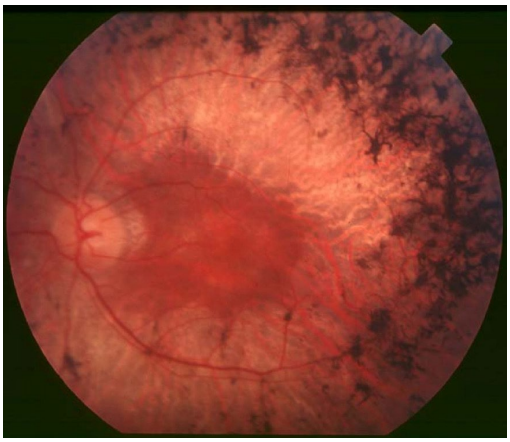


*Figure 5b*. Fundus of retina with RP. *Credit:* Christian Hamel, CC BY 2.0.

### *Questions*

1. Use Figures 6a, 6b and 6c on the following pages to review normal ear function. Use Figures 7a and 7b to review normal eye function. Tell which parts still work in people with Acadian Usher syndrome. Draw an arrow to where harmonin is located in each ear and eye diagram (including Figures 5a and b).

2. Why don't hearing aids help people with Acadian Usher syndrome?

3. Most children born profoundly deaf today receive cochlear implants. Where are cochlear implants surgically inserted? Add a line to the relevant diagrams to represent where the cochlear implant would be. Would a cochlear implant help Dan or Annie if they received one today? Why or why not? Why might people in the Deaf community be opposed to cochlear implants?

4. Describe the likely stages of Dan's or Annie's vision through their adolescence and adulthood, including what their ophthalmalogists likely saw in their retinal exams.

5. *Extension:* Usher syndrome types 2 and 3 cause milder deafness and much later loss of peripheral vision. How can this be explained, now that you understand more about the cellular basis of hearing and vision?

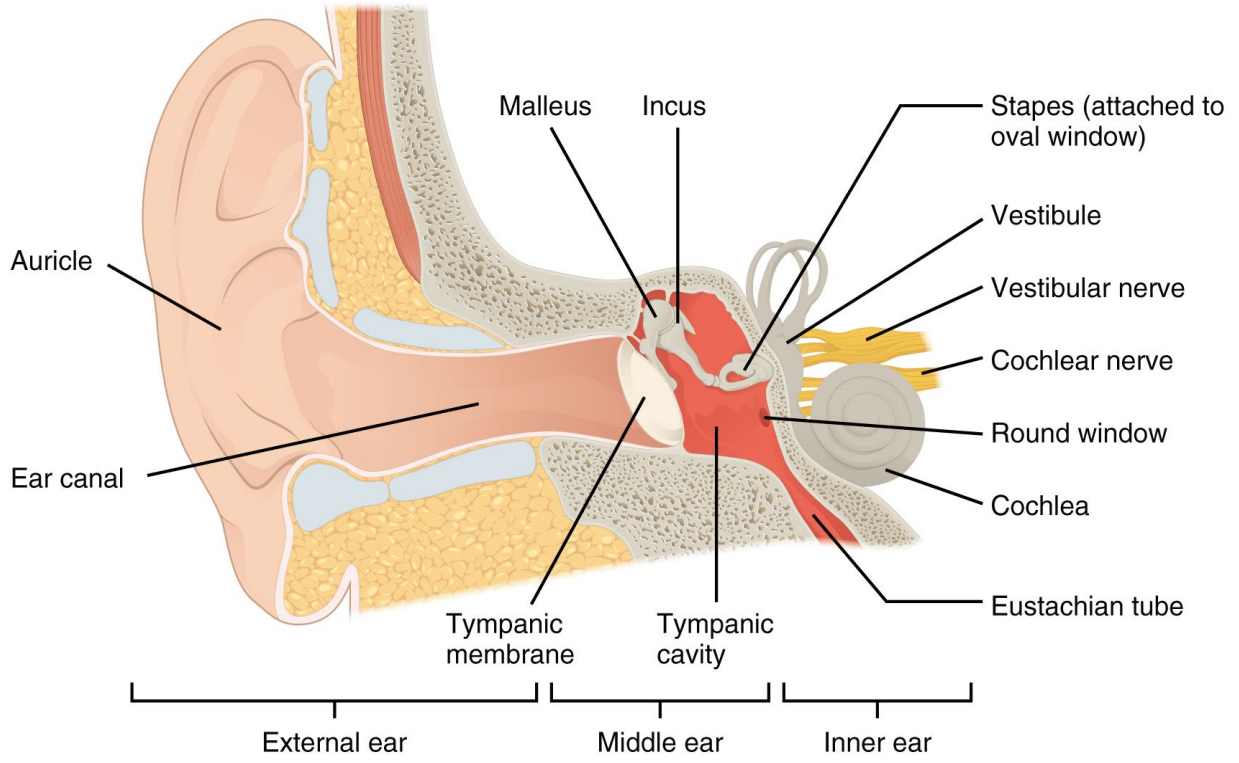



*Figure 6a*. The structures of the ear. *Credit:* OpenStax, CC BY 4.0. Access for free at <https://openstax.org/books/anatomy-and-physiology/pages/1-introduction>.

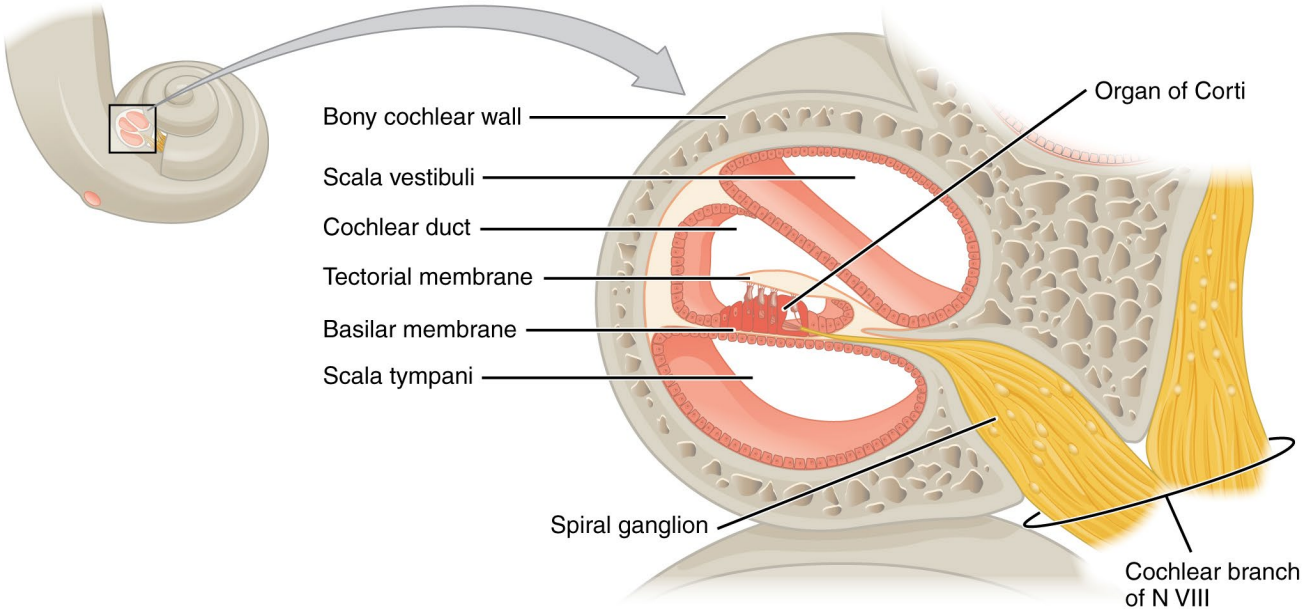



*Figure 6b.* Cross-section of the cochlea. *Credit:* OpenStax, CC BY 4.0. Access for free at <https://openstax.org/books/anatomy-and-physiology/pages/1-introduction>.

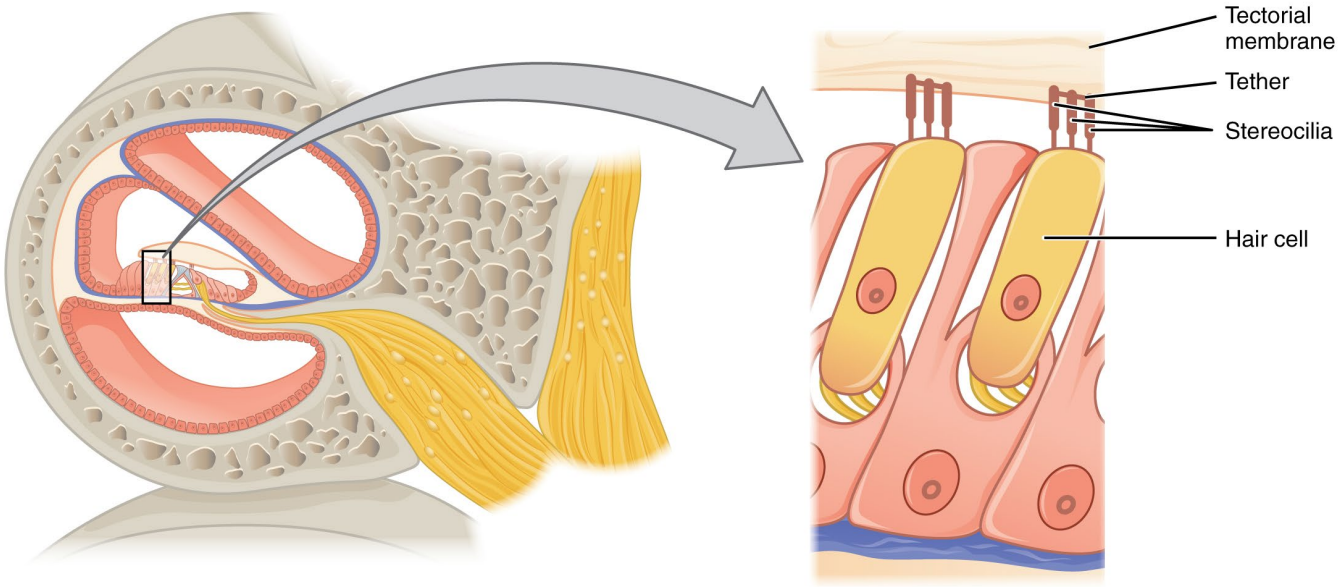



*Figure 6c.* Fine structure of the Organ of Corti. *Credit:* OpenStax, CC BY 4.0. Access for free at <https://openstax.org/books/anatomy-and-physiology/pages/1-introduction>.

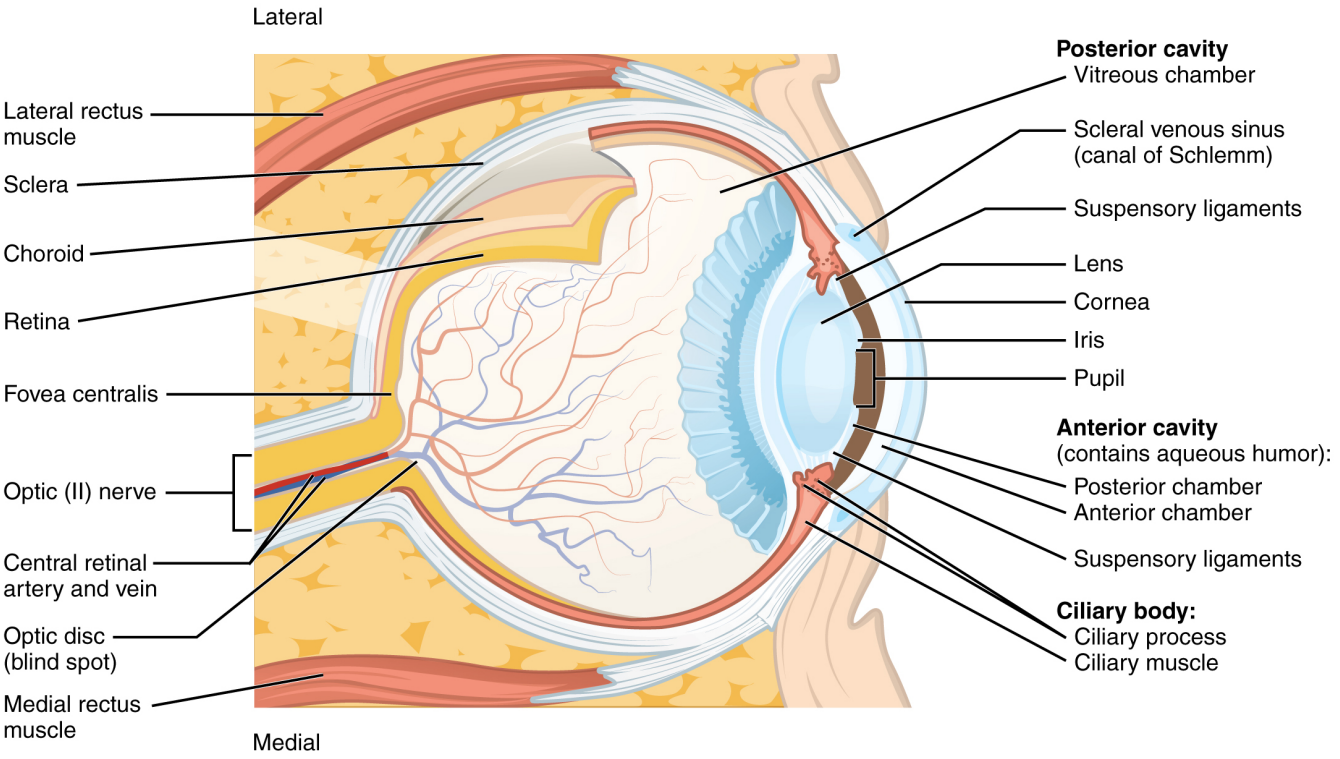



*Figure 7a.* Cross-section of the eye. *Credit:* OpenStax, CC BY 4.0. Access for free at <https://openstax.org/books/anatomy-and-physiology/pages/1-introduction>.

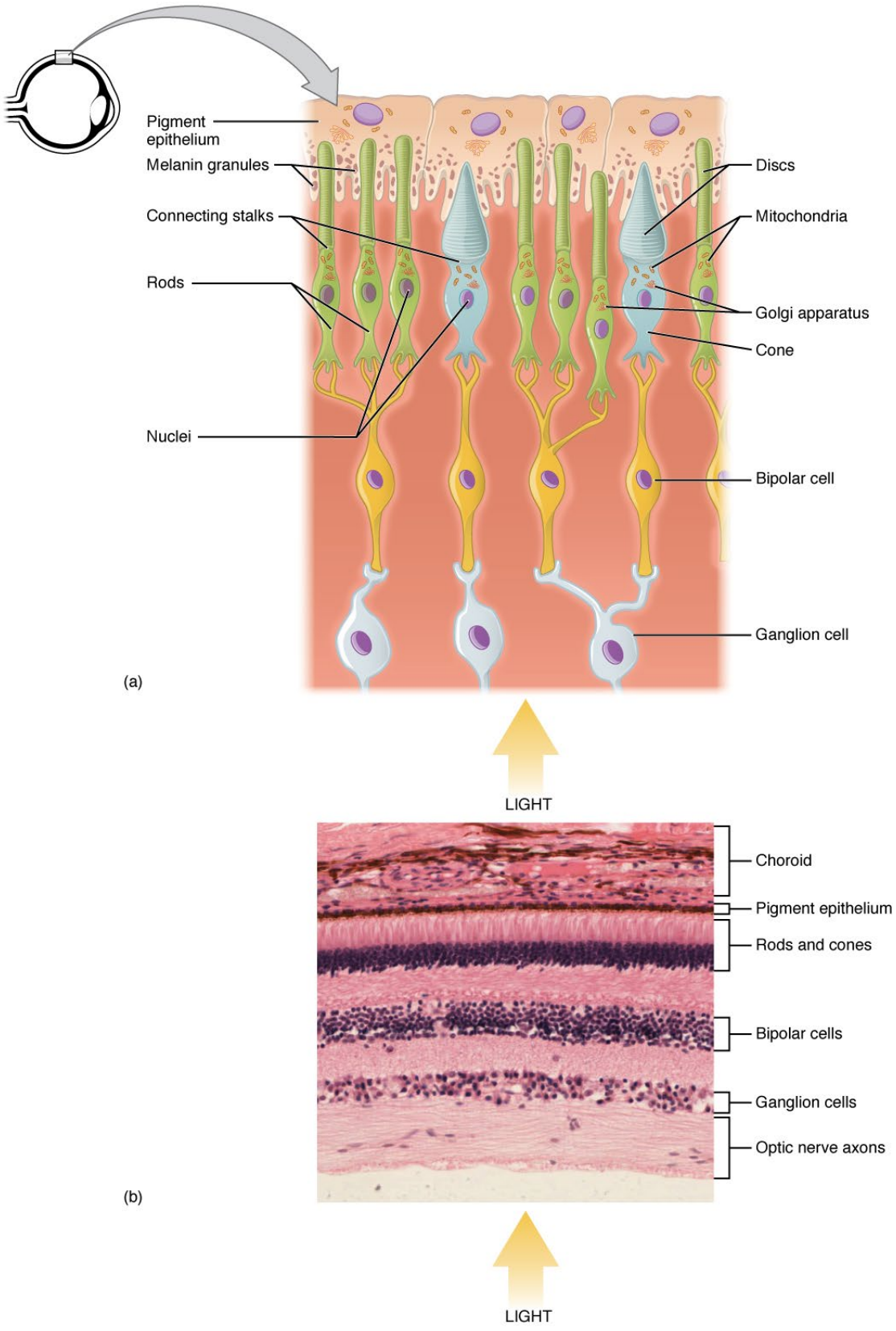



*Figure 7b.* Photoreceptors in the retina. *Credit:* OpenStax, CC BY 4.0. Access for free at <https://openstax.org/books/anatomy-and-physiology/pages/1-introduction>.

## Part III – Usher Syndrome in Families

In the 1970s, geneticists at Louisiana State University Health Sciences Center interviewed dozens of families of students enrolled at the Louisiana School for the Deaf who had been diagnosed with RP in school eye exams. Dan's parents were among those interviewed. The researchers produced large, detailed pedigree charts for each family (e.g., Figure 8) that are now protected in the archives of the medical library. Pedigree charts show each individual in a family tree and their phenotype. Such charts enabled researchers to characterize the inheritance pattern of Acadian Usher syndrome.

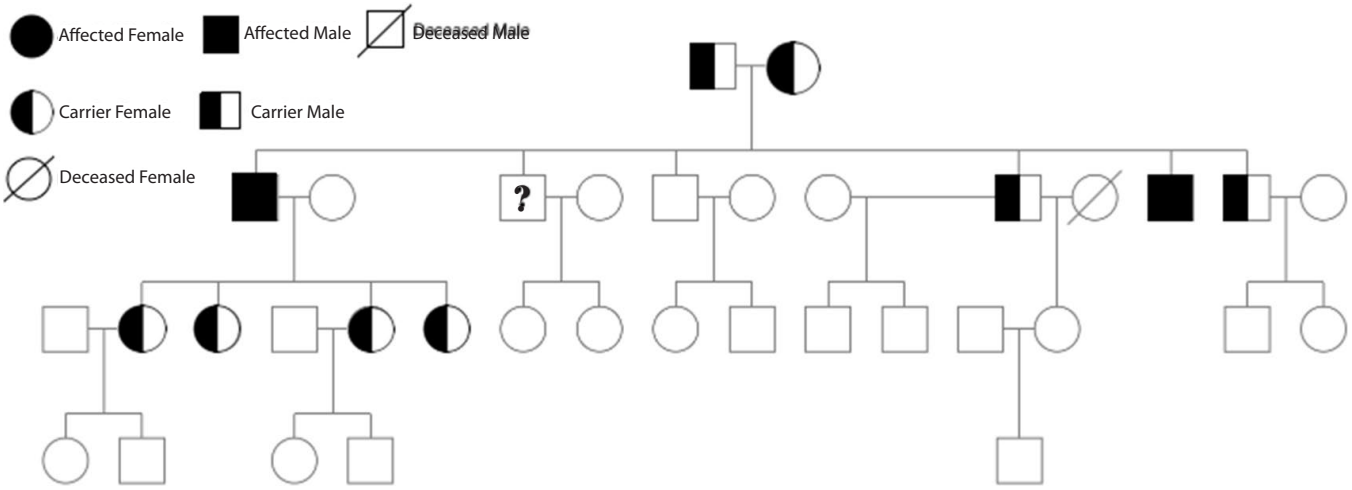



*Figure 8.* Pedigree chart of Dan's family; his parents are at the top. Dan is their oldest child.

### *Questions*

1. Use the pedigree chart to describe Dan's family. Dan is the oldest of his siblings. How many siblings, nieces, nephews, children, grandchildren does he have, and which are deafblind? Which are definitely carriers? (Annie is not represented in this pedigree chart because Dan had his four daughters with his first wife, who was deaf, but not deafblind.)

2. Based on this pedigree chart, can you conclude whether the inheritance pattern for Acadian Usher syndrome is autosomal dominant, autosomal recessive or sex-linked recessive? Can you rule out any?

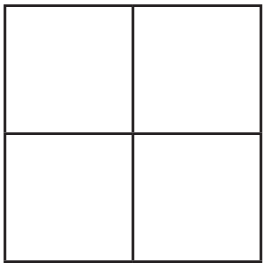
3. Draw a pedigree chart for three generations of Annie's family using this information.
   - Annie's parents were deafblind; her mother is still living.
   - Annie was previously married to a deaf man, with whom she had two sons, both hearing. One son is still living.
   - Annie's older sister is deafblind and is married to a deaf man and has three sons and one daughter, all who hear.
   - Annie's younger brother is deafblind and is married to a hearing woman; they have a son and daughter who hear.

4. Based on both pedigree charts, can you now conclude whether the inheritance pattern for Acadian Usher syndrome is autosomal dominant, autosomal recessive or sex-linked recessive? Can you rule out any?

5. Explain why geneticists usually need many pedigree charts to determine inheritance patterns.

6. *Extension:* Explain how molecular genetics research benefits from classical strategies like pedigree charts.

7. Biologists often use a Punnett square to represent the genotypes expected in the children of two parents. Produce a Punnett square to represent the children possible from Dan's parents. Use the uppercase letter *U* to denote the normal, dominant allele and the lowercase, underlined *u* to denote the Usher, recessive allele.
   - First, write the genotypes of Dan's parents. Dan's parents had to both be carriers (heterozygous), therefore both of their genotypes are *Uu*.
   - Separate each parent's alleles as headings on the two sides of the Punnett square. Write *U* and *u* in the appropriate positions on the Punnett Square (father at top, mother on left side). Consider how Dan's parents' *U* and *u* alleles were segregated during meiosis when they produced their sperm and eggs.
   - Fill in the possible zygote genotypes in the four boxes by stating "If this sperm fertilized this egg, the zygote would be…".



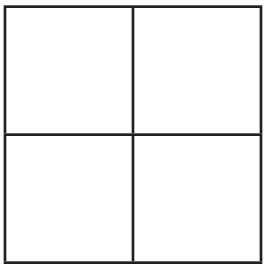
8. Which of the boxes in the Punnett square would represent Dan?

9. Dan and one of his five brothers are deafblind. Only one brother is neither deafblind nor a carrier. Is this about how many you would expect from two carriers? (One brother's carrier status is unknown.)

10. If Dan's parents had had one more child, what is the probability that this child would have been deafblind? (Probability can be represented as a fraction, decimal or %.)

11. Is it possible for Dan's parents to have had no deafblind children at all? If so, what is the probability that could have happened?

Draw another Punnett square to represent Annie's family. Annie's parents and all three of their children are deafblind.



12. Is it possible for Annie's parents to have had no deafblind children at all?

13. If Dan and Annie had children together, what fraction of their children would have been deafblind?

14. *Extension:* Dan's daughters know that they are carriers. What is the probability that Dan's grandchildren inherited the Acadian Usher allele? How would the probability be different if Dan's sons-in-law had Usher syndrome in their families? What is the probability that Dan's first cousin (the author) is a carrier?

## Part IV – Chromosomes and Cell Division

Dan and Annie understand that the cause of their deafblindness lies in their chromosomes and runs in their families. Like most humans, they have 23 pairs of chromosomes in the nucleus of all their somatic (body) cells, which can be visualized in a karyotype, a set of photographs of a single cell's chromosomes taken with a microscope (Figure 9). These cells are rapidly dividing epithelial cells, therefore many cells will be in a stage of mitosis in which the chromosomes are condensed (late prophase or early metaphase) and therefore easy to see. The technician fixes cells onto a slide, squashes and stains them, then uses imaging software to digitally cut out the chromosomes and line them up by size, largest to smallest.

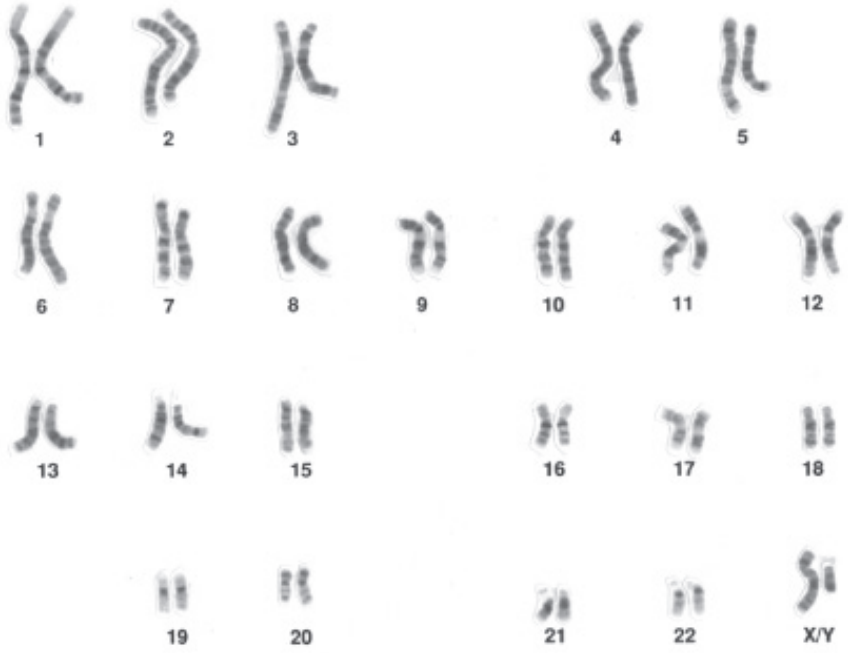



*Figure 9.* Human karyotype. *Credit:* National Human Genome Research Institute, PD, <https://en.wikipedia.org/wiki/File:Human_male_karyotpe.gif>.

### *Questions*

1. Each of the 46 chromosomes shown here is already replicated, therefore each chromosome in a karyotype is composed of two identical sister chromatids. The two strands of the "X" are tightly attached at a centromere and along the length of the chromatids. Knowing this, how many molecules of DNA are shown in this karyotype? (each double helix is considered one DNA molecule).

2. Was the cell used for the karyotype above diploid or haploid? How do you know?

3. Notice that each homologous pair of autosomes is numbered. In pair #11, mark one chromosome P to represent the paternal chromosome and M to represent the maternal. Are the chromosomes in a homologous pair identical?

4. Is this a karyotype of a human male or female? How do you know?

5. Where is the *USH1C* gene located in the human genome? To find out, visit Online Mendelian Inheritance in Man (OMIM, <http://www.omim.org/>). Type "Usher syndrome" in the search field. Click the Acadian Usher syndrome entry. What is the cytogenetic location of the *USH1C* gene? What does this mean?

6. In the karyotype image above, mark the locus of the *USH1C* gene on both chromosomes. Imagine this karyotype is for Dan's father. Based on family history, Dan's father probably inherited the allele from his mother's side. Mark a *U* and u on the respective chromosome 11s.

7. Can someone's *USH1C* genotype or carrier status be determined using this karyotype?

8. Can a karyotype be made using a semen sample?

Apply your understanding of meiosis I and II in spermatogenesis and oogenesis to explain how Dan inherited the same *USH1C* gene variant (allele) from his parents. By chance, the sperm and egg that formed zygote Dan both carried the *u* allele.

9. How many sperm are in a typical human male ejaculate? In Dan's father, how many of these sperm carried the *U* allele? How many carried the *u* allele?

10. Most women produce one egg per month. Use your knowledge of the menstrual cycle and oogenesis to explain how Dan's mother produced an egg carrying the *u* allele.

11. Apply your understanding of mitosis to explain how zygote Dan became a multicellular man.

12. Apply your understanding of replication and the cell cycle to explain why all his somatic cells carry two copies of the *u* allele of the *USH1C* gene.

13. Explain which of Dan's cells will undergo meiosis, and why all his sperm will carry chromosome 11 containing the *u* allele.

## Part V – Gene Expression

Both Dan and Annie are homozygous recessive (*uu*) for the *USH1C* allele of a gene that encodes a protein called harmonin. Like all proteins, harmonin is produced by transcription and translation. For this activity, open, but do not print, the document deafblind_sequence.doc. (Your instructor should provide you with this file). This document contains the complete sequence of the coding strand of the normal *USH1C* gene. (You can verify this at <https://www.ncbi.nlm.nih.gov/genbank/>. Search for "Human *USH1C*" and choose "RefSeqGene.")

### *Questions*

1. How many nucleotides are in the intact *USH1C* gene?

2. Write the first 30 nucleotides of the *USH1C* gene below. Write 5′ on the left end and 3′ on the right end. Label this the "Coding Strand." Write the complementary strand under it, using the A-T, G-C base-pair rules. Write 3′ on the left end and 5′ on the right end. Label this the "Template Strand."

#### *Transcription*

3. Which strand of the DNA is copied by RNA polymerase, the template or coding strand?

4. Predict the sequence of the primary RNA transcript of the above 30 base pairs of the *USH1C* gene and write it below. Write 5′ and 3′ on the appropriate ends. (Note that the primary transcript is not called "mRNA" until it has been processed and is ready for translation.)

5. Did you write 5′ on the *left* or on the *right* end of the Ush1c RNA transcript? (Notice the change in format from *USH1C* to Ush1c. *USH1C* refers to the gene. Ush1c refers to the transcript.)

6. Does the primary transcript look more like the template strand of the DNA or the coding strand?

#### *Processing*

7. Before editing the sequence, count and record the number of exons (brown sections).

8. Delete all the introns and row numbers. Rename and save this file. The remaining exons are spliced together to form the mRNA. How many nucleotides remain in the mature Ush1c transcript after processing? (Use the Word Count tool to count "characters without spaces.")

9. What fraction of the total mRNA was removed during processing?

10. What else happens to the mRNA during processing?

11. What happens to the mRNA after processing?

12. *Extension:* Several mRNA variants are produced from the primary transcript by alternative splicing. The brown exons in the *USH1C* gene in the worksheet are those in variant 1. You can see other variants by exploring the *USH1C* entry in GenBank. These mRNA variants create multiple isoforms of the harmonin protein in different cells at different times.

### *Translation of Harmonin*

The GenBank sequence you began with represents the gene in its DNA form. To continue, change each "T" to "U" using the "find and replace" tool in Word.

13. Find the start codon AUG by reading the nucleotides one letter at a time. Circle the first AUG you find and label it "Start Codon." The A of the start codon is at nucleotide #___ (*Tip:* use Word's Find tool to help you find the first AUG.)

14. Which amino acid is encoded by AUG in the mRNA? Give the full name: _____, the three-letter abbreviation: ____**,** and the one-letter abbreviation: ___ for this amino acid. This becomes the first amino acid on the N-terminal end of every protein. Is AUG the only codon that codes for this amino acid? ____ Can this amino acid be found within a protein as well as the beginning? _____

15. Underline the first 10 codons in the mRNA in your edited sequence. Use a genetic code table to translate these to the first 10 amino acids of harmonin. Write them as a polypeptide below with a dash between amino acids to represent the peptide bonds.

16. Translation will continue until the ribosome reaches a stop codon (UAG, UGA or UAA) and falls off the mRNA. Find and mark the stop codon in your mRNA file. How many amino acids are in this variant of the harmonin protein?

17. Is the entire mRNA translated? Or are there extra untranslated regions of the mRNA before the start codon and after the stop codon?

18. Check your amino acid sequence by going to <https://web.expasy.org/translate/>. Copy your mRNA sequence into the field. It will return three reading frames read in both directions, so six total. Choose the option that has the longest open reading frame. Check your start and stop codons, amino acid number and spot check the amino acid sequence you got when you translated using the genetic code. Did you make any mistakes? Do you think the ribosome makes mistakes? What would happen if it did? Could this be how the mutation first arose in Dan and Annie's ancestor? Explain.

19. *Extension:* How would alternative mRNA splicing change the amino acid sequence?

At this point, the primary protein structure is complete, the ribosome falls off and the protein adopts its secondary and tertiary structure.

20. Go to the RCSB Protein Data Bank at <http://www.rcsb.org/pdb> and search "harmonin." Some protein structures in this database are partial. If possible, locate the N-terminus, C-terminus and any alpha helixes, beta sheets or disulfide bridges in those structures.

### *Dan and Annie's USH1C Alleles*

21. Return to your processed mRNA file. Find and mark nucleotide #216 after the first AUG (count the A of AUG as #1). Verify that this nucleotide is a G.

The wild type Ush1C transcript has a Guanine at position 216, which is replaced with an Adenine in the Acadian Usher allele (called "216 G to A"). This mutation creates a faulty splice site that causes the primary transcript to be processed incorrectly. It also causes a reading frame shift that creates a stop codon. Therefore the harmonin in Dan and Annie's retinal and cochlear cells is too short (truncated). It is not yet known whether the cell degrades this misformed protein or it persists, nor known whether carriers (heterozygotes, *Uu*) express both the normal and mutated harmonin.

### *A Genetic Cure?*

Like many who are born profoundly deaf, Dan and Annie do not lament their inability to hear. They feel that their language and community are rich and supportive, and their lives are full. However, their loss of vision significantly affects their ability to live independently. They must rely on others to drive them to and from work, church and social activities. Most parents of young children with Usher syndrome have chosen cochlear implants for their children, but are worried about the future of their children's vision. They are keen to find a treatment that slows progression of RP.

To better understand Acadian Usher syndrome, Dr. Jennifer Lentz from Louisiana State University Health Sciences Center developed a knock-in mouse line that has the exact 216 G->A Acadian allele. These research mice have the same phenotype as deafblind Cajuns: profound congenital deafness, balance problems and eventual blindness due to RP. Dr. Lentz designed an anti-sense oligonucleotide (ASO) that prevents deafness and blindness in her knock-in mice. ASOs are morpholinos, a chemically modified DNA that is not readily broken down in living cells. The mice treated with the ASO before birth are not deaf, do not develop RP and do not have balance problems.

22. How do you think Dr. Lentz knows whether her mice can hear and see?

23. What sequence of nucleotides in your *USH1C* gene worksheet do you think Dr. Lentz chose for her ASO?

24. Do you think Dan and Annie could benefit from ASO treatment if given today?

The FDA has approved direct injection of other ASOs into the human eye to treat other genetic eye diseases. Testing of the Acadian Usher ASO for safety and efficacy in humans is still a long way off, however. (The challenges involved are summarized at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/>.) Bringing a treatment to market is also expensive. Parents of children with Usher syndrome have launched several non-profit organizations to raise money that might bring a cure soon enough to slow their children's blindness.

25. What do you think are the barriers that must be overcome before Usher patients can be treated with ASOs or other genetic therapies?

26. Can patients with other forms of RP or Usher syndrome benefit from Dr. Lentz's ASO therapy? Why or why not?

27. If this approach works in humans, will this stop the Usher syndrome allele from being passed down to future generations?

28. Why are researchers focused more on preventing blindness than deafness?

29. *Extension:* Joanie and Cory (Figure 10) are twins who have Usher syndrome. They are compound heterozygotes, which means they have two faulty *USH1C* alleles, but they are different alleles. They each got the 216 G->A allele from their mother, of Acadian descent, and the 238-239 ins C allele from their father, of German Jewish descent. Do you think they can still benefit from Dr. Lentz's ASO treatment designed for the Acadian allele? Why or why not?

*Figure 10.* Joanie and Cory are twins with Usher syndrome due to two different *USH1C* alleles. *Credit:* Usher 2020 Foundation, used with permission.

## Part VI – Where the Acadian Allele Came From

Dan and Annie's families are both of Acadian descent. The Acadian *USH1C* allele came with the first Acadian settlers to southern Louisiana in the late 1700s. Acadians were French-speaking colonists of eastern Canada who were exiled by the British. Some Acadians returned to France, some settled along the Atlantic coast of what would become the United States, and many settled in the French parishes of the Louisiana territory now known as Acadiana (Figure 11). The descendants of the Acadians and others who settled this French-speaking region are now known as Cajuns. By chance, a higher number of *USH1C* carriers were among this founder population. As a result of this founder effect and centuries of geographic and cultural isolation due to language and religion, the DeafBlind population in Louisiana is now the largest in the U.S. and the second largest in the world. Even though there are hundreds of DeafBlind citizens in Louisiana, it is still a rare condition. There are still DeafBlind citizens in Canada and along the Atlantic US coast who share the same 216G->A allele.

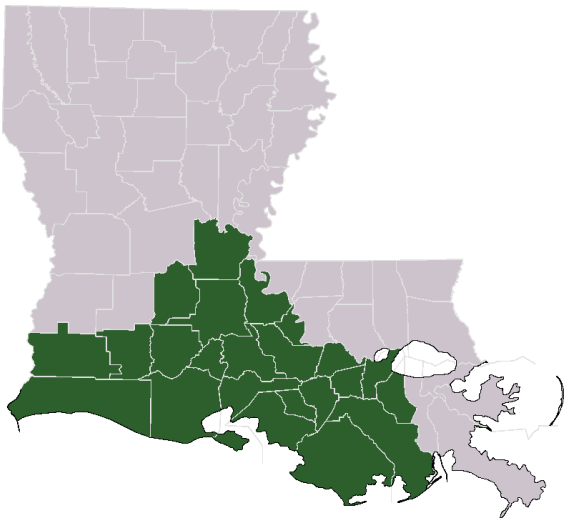


*Figure 11.* Acadiana parishes of Louisiana. *Credit:* Quartier-Latin1968, CC BY-SA 3.0.

We can estimate the carrier frequency for the 216 G->A *USH1C* allele in Acadiana based on a few facts about the population. According to a recent census, the population of Louisiana was 4,681,666.

### *Questions*

1. If approximately 1/3 of Louisiana citizens live in Acadiana parishes, how many people live in Acadiana?

2. About 70,000 Louisiana citizens are deaf. Assuming that the deaf population is equally distributed in the state, approximately how many deaf people live in Acadiana?

3. According to estimates from the Deaf community, about 10–20% of the Deaf in Acadiana are DeafBlind, which is at least _____ people. This is approximately equal to 1 DeafBlind person for every ____ citizens in Acadiana, or ____**%** or _____ (decimal) (This is $q^2$ referenced below.)

4. The population of Acadiana is a mixture of deafblind (*uu*), carriers (*Uu*) and neither (*UU*). Use the Hardy-Weinberg equation $p^2 + 2pq + q^2 = 1$ and the value of $q^2$ above to estimate the remaining fraction or % of Cajuns that are *UU* ($p^2$) and *Uu* ($2pq$).

5. If you are in Acadiana and encounter 1000 different, random people in a given month, how many would be DeafBlind? (Assume that DeafBlind people are just as likely to be encountered in public places as hearing/sighted people.)

6. If you are in a lecture hall with 300 students from Acadiana, about how many of these people might be carriers of the Acadian *USH1C* allele?

7. Why do you think the Acadian Usher allele is in higher frequency in Louisiana than elsewhere?

Hardy-Weinberg equilibrium predicts that the allele frequencies (and therefore genotype frequencies) in a population's gene pool will remain constant over generations unless it is evolving due to one or more of the following five conditions:

1. There is no natural selection for or against the *USH1C* allele.
2. The population is large enough to buffer changes and genetic drift, including the founder effect.
3. Mating is random; in other words, those with *USH1C* allele do not select or reject mates based on their phenotype.
4. No new mutations form in this gene.
5. No new alleles enter by migration (gene flow).

## *Questions*

8. The population of Acadians who settled in Louisiana was several thousand people who, by chance, had a higher frequency of carriers of the 216 G->A allele than the source population in Canada where the mutation arose. The gene pool of this small founder population was not representative of the original population, thus violating condition #__ above, and causing the gene pool of Acadian settlers to change over time (evolve).

9. The Acadians spoke French and were of Catholic faith, therefore tended to marry within this large community. This met condition #__, which helped to maintain equilibrium of the *USH1C* allele at a higher level in Louisiana.

10. Once Deaf children began to be educated together in state schools in the 20th century, they married and had children with other Deaf people. These circumstances of language, religion and education violates condition #__ above, which may have caused the frequency of the *USH1C* allele to increase over several generations.

Similar conditions explain regional genetic differences in all populations of all organisms, not just DeafBlind Cajuns.