The “Wolfman” and the Chromosomal Basis of Heredity

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The Case

We've all heard the werewolf legend – when the moon grows full, a man is transformed into a beast that grows hair and acquires awesome powers.

But what if it weren't the light of the moon that gave the werewolves of legend all that hair?

Danny Ramos Gomez has a condition called *hypertrichosis* that causes his body to produce an abnormal amount of hair everywhere, which is why people call him “the wolf man.”

http://abcnews.go.com/Primetime/Video/playerIndex?id=2264698
Hypertrichosis

- Hypertrichosis is a rare genetic condition (only 50 documented cases since the Middle Ages).
- Excessive growth of hair, and hair in areas of the body that do not normally grow hair.
- There are several different forms of the disease.
- A genetic disease, it can be inherited.
History of the disease

• Historical hypertrichosis has attracted human attention.

• Many affected individuals became “exhibitionists.” One of the most famous was the Russian, Theodoro Petrov, who was known as Jo-Jo the “Dog-Faced Boy.”

• Danny Gomez and his brother Larry were part of a freak show as children; they were exhibited like animals and called “wolf children.”
How did the Gomez brothers inherit hypertrichosis?

a little genetics....
Chromosomes and DNA structure

- Deoxyribonucleic acid (DNA) is a double helix made up of two strands of nucleic acid comprised of the nitrogenous bases adenine (A), thymine (T), cytosine (C), and guanine (G).
- Each strand complementary base pairs with the adjacent strand
  - \( A : T \)
  - \( C : G \)
- Strands have orientation (5’ and 3’ ends) and exist anti-parallel.
- DNA is organized into genes; each gene codes for a particular trait, e.g., eye color.
- DNA cannot fit into the nucleus of a cell this way so it is tightly packaged into chromatin and ultimately chromosomes.
CQ#1: Look at the following sequence and identify the complementary strand:

5’ TTACCGGGTCCAGTCATGCGA 3’

A. 5’ TTACGGGTTCCAGTCATGCGA 3’
B. 5’ TCGCATGACTGGACCCGGTAA 3’
C. 5’ AGCGTACTGACCTGGGCATT 3’
D. 5’ TGCTTTAGGATGGGATAGCATG 3’
Karyotypes

- A karyotype is an organized profile of an individual’s chromosomes. In a karyotype, chromosomes are arranged and numbered by size, from largest to smallest.
- Humans have 46 chromosomes or 23 pairs.
- 22 of these pairs are **autosomes**.
- 1 pair are **sex chromosomes**, X and Y.
- An XX person = female; an XY individual = male
CQ#2: Based upon the karyotype below, is the individual a male or female?

A. Male
B. Female
Meiosis and fertilization review

• Meiosis is the process in humans by which haploid gametes are formed.
• **Gametes** are sperm (male) and egg (female).
• During **fertilization**, haploid gametes fuse to form an embryo.
• Danny Gomez received one set of chromosomes (**haploid**; n) from his mother and a second haploid set from his father, therefore he (and all humans) is a **diploid** (2n) organism.
• If a chromosome in one gamete has a mutation in a particular gene (like the gene linked to hypertrichosis), the mutation may be passed on to the offspring.
Do both alleles have to be mutated to get hypertrichosis?

- Alternative variations of genes = **alleles**.
  - Alleles can be dominant or recessive
- Two mutant alleles are required to express a recessive trait or **phenotype**.
- One mutant allele is required to express a dominant trait or phenotype.
- A person who has two alleles that are the same for a particular trait is said to be **homozygous**, whereas two different alleles for the trait would be **heterozygous**.
Dominant and Recessive

- Dominant alleles are written with a capital letter, for example: B.
- Recessive alleles are written with a lower-case letter, for example: b.
- A heterozygote would be Bb and homozygotes would be BB or bb.
- Offspring can be predicted using a **Punnett Square**.
CQ#3: How many different genotypes are possible from the cross Aa x Aa? Phenotypes?

A. 1; 1
B. 3; 2
C. 2; 3
D. 4; 4
Some hypertrichosis is autosomally inherited

- Genetic diseases that result from mutations on an autosome can be either **autosomal dominant** or **autosomal recessive**.
- Autosomal hypertrichosis is **dominantly** inherited.
- Mutations on chromosome 8 have been identified with this type of hypertrichosis.
Inheritance Patterns

Autosomal recessive

Carrier father  
Carrier mother

Unaffected  
Affected  
Carrier

Unaffected  
Carrier  
Carrier  
Affected

Unaffected  
Carrier  
Carrier  
Affected

Autosomal dominant

Affected father  
Unaffected mother

Unaffected  
Affected  
Unaffected

Affected  
Unaffected  
Unaffected  
Affected

U.S. National Library of Medicine
CQ#4: A male who is a heterozygous carrier for an autosomal recessive disease marries a homozygous unaffected female. What is the chance of having an affected child? A child who is a carrier?

A. 50 %; 50%
B. 0%; 50%
C. 50%; 0%
D. 25%; 50%
Sex linked genes

• In addition to their role in determining sex of an organism, X and Y chromosomes have many other genes that are unrelated to sex.

• A gene on either sex chromosome is call a **sex-linked gene**.

• Congenital generalized hypertrichosis (CGH), the type that Danny Gomez has, is **X-linked dominant**; the gene that is mutated is found on the X chromosome.

• Sex-linked mutations can be either dominant or recessive.
CQ#5: A man who carries an X-linked allele will pass it on to:

A. All of his sons.
B. All of his children.
C. Half of his daughters.
D. All of his daughters.
E. Half of his sons.
Danny’s Pedigree

- A pedigree is a family tree showing genetic relationships for a particular trait.
- In a pedigree:
  - Horizontal lines = matings.
  - Vertical lines = offspring.
  - Squares = males.
  - Circles = females.
  - An individual with the trait being followed is shaded.
CQ#6: Based upon the ABC News story, all of the males in Danny’s immediate family have CGH. His sister Jaime also has the disease. This indicates that Danny inherited the mutant allele from his:

A. Mother  
B. Father
CQ#7: Assuming Danny’s father is phenotypically normal, would it be possible for Danny to have a completely unaffected sister? Why?

A. Yes; if the mother is heterozygous, she could inherit a non-mutant X chromosome from her mother and a non-mutant X from her father.

B. No; she can only inherit a mutant X chromosome from her mother and a non-mutant X from her father.

C. No; she can only inherit a mutant X chromosome from her mother and a Y chromosome from her father.
CQ#8: Look at Danny’s pedigree again. What is the genotype of his mother?

A. XX
B. XX
C. XX
D. XX or XX
Probabilities

- The rules of probability can be applied to predicting genetic outcomes.
- Tossing a coin illustrates rules of probability.
- Probability of a heads = $\frac{1}{2}$ and probability of tails = $\frac{1}{2}$.
- Multiplication rule can be used to predict the probability that two coins would land heads up
  - $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$.
CQ#9: If you have a coin, take it out and flip it. Indicate whether you flipped a heads or tails.

A. Heads
B. Tails
CQ#10: Flip your coin again. Indicate whether you flipped a heads or tails.

A. Heads
B. Tails
Ok, now based upon the total number of students that flipped a coin, calculate the % heads and % tails.

Why did we not get 50% heads and 50% tails?
CQ#11: If Danny ever has a son, what is the probability of that child having hypertrichosis?

A. 100 %
B. 50 %
C. 25 %
D. 0 %
WHY?

- Because the mutation is X-linked.

- Probability of Y for a son = 1/1
  - To have a boy, the father must contribute the Y chromosome.

- Probability of X for a son = 0/1
  - In boys, the mother always contributes the X chromosome, not the father.

- **0 chance**
Why do many of the females in Danny’s family have varying degrees of the disease?

- Female humans inherit two X chromosomes; only one is active in each cell.
- The other X chromosome becomes inactivated during embryogenesis via the process of X inactivation -
  - Also call *lyonization*.
- The inactivated X is called a **Barr Body**.
- Selection of which X will be inactivated is random.
- As a result, in women with hypertrichosis, some cells express the mutant X-linked gene and some do not, thus resulting in a mosaic effect.
Atavism

• Hypertrichosis is sometimes considered an atavism—a trait that reappears once it has disappeared generations ago.

• Atavisms likely occur as a result of mutation, but can also happen by gene rearrangements.

• There is a difference between atavism and vestigial structures.
  – Vestigial structures are body parts that survive as degenerate, imperfect versions of what they should be.

“Dolphin reveals an extra set of ‘legs’ -- Scientists say fins may represent throwback to ancient land-dwelling ways”

By Hiroko Tabuchi, updated 3:44 p.m. ET, Mon., Nov. 6, 2006
TOKYO - Japanese researchers said Sunday that a bottlenose dolphin captured last month has an extra set of fins that could be the remains of hind legs, a discovery that may provide further evidence that ocean-dwelling mammals once lived on land.
http://www.msnbc.msn.com/id/15581204/