Chimerism: The Stranger Inside You

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Objectives

At the end of this presentation, the attendee should be able to:

► Clearly define the term chimerism (from Greek mythology to current-day).

► Have a general understanding of the possibilities of how human chimeras can exist.

► Explore the possibilities of seeing an increase in chimeras in the normal population.
In Greek mythology, Homer described the chimera in the *Iliad* as “a thing of immortal make....not human, lion-fronted and snake behind, a goat in the middle.” It supposedly roamed the countryside of Asia Minor, terrorizing the Lycians, bringing volcanos, shipwrecks and “snorting out breath with a terrible flame of bright fire.”
Chimerism: Looking Ahead

Chimerism in the human species has already popped up in the form of popular culture.

The novel “Next” written by Michael Crichton (of Jurassic Park).

Popular TV shows such as CSI and House both featured plots with chimerism.

The public loves intense “scientific” plotlines, but how realistic are they?

Even though human chimerism is quite rare, there have already been 30 to 40 documented cases since 2003.
Chimerism: Vanishing Twin

► Most all human chimeras were, at one time, fraternal twins. Genetic chimeras develop spontaneously when fraternal embryos fuse or when one twin absorbs the other. The absorption process is known as Vanishing Twin Syndrome.

► In very rare conditions, the DNA of a lost embryo in utero can actually turn a mother into a chimera, perhaps a manifestation of grief; in a defiant refusal to let go, her body will actually absorb its tissue, retaining her loss and invisibly altering her body into a kind of living memorial.
Mosaicism vs. Chimerism

Mosaicism - the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilized egg.

Chimerism - contain two or more genetically distinct genotypes that are originated from the fusion of two or more different zygotes.
Types of Chimerism

Microchimerism vs. Tetragemetic Chimerism
Microchimerism

- Microchimerism, a smaller degree of chimerism, may arise from organ transplants and blood exchanged by twins in utero.

- Studies show that there is increasing evidence that many people may actually be microchimeras because their bodies contain cells genetically identical to their older siblings (maternal siblings only, since these cells are passed to them because their mother retained them).

- During pregnancy, the blood of the mother and fetus are kept separate, but the placenta is an imperfect barrier and some cells slip through. Children pick up some cells from their mother and she picks up some fetal cells.

- 80-90% of women carry their children’s cells or DNA in their blood during pregnancy. Up to 50% carry them for decades after giving birth. Some of those cells may slip from the mother’s bloodstream into the body of the next child. Some cells may even pass from her children into her grandchildren.

- For some reason, our immune system tolerates these cells in the blood and may be an essential part of preventing a rejection of the fetus. Some of those maternal cells may become incorporated into the body tissues of the fetus where they may be associated with autoimmune diseases.

- Though most chimeras tend to be female, it is possible for a man to be a chimera. His blood may actually contain different DNA from his testes. This would certainly reek havoc on paternity testing. “YOU ARE NOT THE FATHER, might actually be: WELL, YOU MIGHT BE, WE’RE NOT QUITE SURE”!
Tetragametic Chimerism

- The tetragametic chimera arises from 4 gametes: 2 eggs fertilized by 2 sperm, resulting in dizygotic twins who fuse into one individual.
- When the zygotes fuse, it forms an organism that has two distinct cell lines, and the resulting fetus may be male, female, or hermaphroditic.
- It usually occurs with fraternal (dizygotic) twins and increases with In-Vitro-Fertilization.
- As a result, the individual may have “populations” of cells: one set of DNA may appear in the liver, and another set in the lung.
Visible chimeric characteristics usually include patches of pigmented skin shown in the patterns (left); and also in the color of the eyes (right).
Case 1: Mrs. McK

First Identified Human Blood Chimera - 1953

Mrs. McK, from northern England, age 25, gave a blood donation in March 1953. Results revealed that she had blood types O and A.

She had 60% type O and 40% type A. There was no previous blood transfusion and new blood samples excluded the possibility of a mixed sample.

Upon extensive review of her medical history it was revealed that she had a twin brother who died at the age of 3 months from pneumonia.

Cells from her saliva did not produce A antigens, which means that her real blood type is O, so her brother’s cells must have turned to into a chimera. She secreted O (H) antigen in her saliva but does not secrete A antigen. Since the red cells of her twin were A1, Le(a-b+) he must have secreted A.

There was extensive research by the Blood Group Research Unit of London comparing genotypes from all of the surviving family members. It is bizarre that in 1953 they were able to completely group her twin 25 years after his death.
Case 1: Mrs. McK

- The O and A1 cells in her blood could be separated.  
  The O cells are $kk$,  
  The A1 cells are $Kk$, $Jka+b+$

- The early presence of A antigen has presumably inhibited the production of anti-A. Mrs. McK is group O and her serum contains anti-B, but there is no detectable anti-A.

- Secretion of A antigen in saliva clearly must depend on the presence of the genotype of the A gene as well as the secretor gene, for the secretor gene of Mrs. McK cannot command the secretion of A present only in her circulation.

- Mrs. McK is feminine in appearance and has had one child: She is clearly not sterile or a hermaphrodite. It is interesting however having established that there can be prenatal communication between the circulations of dissimilar twins, it may be worth recording the proportion of twins among people suffering from infertility.
Case 2: Dual Gender Chimera

Could human chimeras incorporate twins of two different sexes?

► Many human chimeras show no overt signs of their condition. The incidence of human tetragametic chimerism may be on the increase due to modern fertility treatments that cause women to release multiple eggs or that implant multiple embryos in hope that some will grow.

► In 1998, doctor’s at the University of Edinburgh, UK reported a 4-year-old male patient referred to them for an undescended left testicle.

► Upon surgery, there was no second testicle found. Unexpectedly, what was found was an ovary and fallopian tube on his left side.

► This patient turned out to be genetically two people.
Case 2: Dual Gender Chimera

- Two fertilized eggs had fused into one embryo.

- One egg was XX (female) and the other was XY (male) making some parts of his body genetically female while other parts were genetically male.

- He was outwardly male, but had a partial womb, fallopian tube and ovarian tissue. He was a chimera formed from the fusion of male and female embryos.

- While this is a dramatic finding, most chimeras show more subtle signs, such as mismatched eyes, or partly-colored hair.
Case 3: Karen Keegan

Meet Boston teacher Karen Keegan, 52, a wife and mother of 3 adult sons.

In 1998, Karen was in urgent need of a kidney transplant and she and her family were tested to find a matching donor.

There was a complete match of her youngest son but no genetic match at all with her two eldest sons. Karen was told that she was not the biological parent of two of her three naturally conceived sons. In the HLA typing, all three sons shared a haplotype with their father, but only one shared Karen’s.

Karen’s two brothers and mother donated blood samples which were sent to Boston. These family tests would be key to the mystery. Comparing the DNA from Karen’s family members led to a bizarre result. It looked as if Karen’s sons were actually descendants of her husband and one of her brothers!

Karen’s case was so intriguing that her physicians got funding for a dedicated research project. They enlisted the help of immunologists at the American Red Cross and Harvard Medical School.

Tests on her hair and skin proved nothing, so doctor’s needed to take samples from her internal organs. She had had some prior surgery and tissue was provided from the pathology department, in particular thyroid tissue and bladder tissue.
Case 3: Karen Keegan

- Having established that her boys were members of this family and carried Karen’s husband’s DNA, it still remained to find the DNA in Karen.
- The testing of the thyroid tissue revealed the missing DNA.
- Karen’s body was made up of two genetically distinct cell lines. There was only one conclusion: Karen was a mixture of two different people.
- Karen is known as a tetragametic chimera, one of only 30 reported cases. Her body is made up from two genetically distinct cell lines derived from a total of 4 gametes – two eggs fertilized by two different sperm.
- Results revealed that the most likely explanation is that Karen’s mother conceived non-identical twin girls, who fused at an early stage of the pregnancy to form a single embryo.
- So one of Karen’s sons came from an egg derived from the twin whose cells dominate in her blood, but her two oldest sons came from eggs whose DNA was compliments of her vanishing twin found only in her thyroid gland.
- Karen’s remarkable story was featured in a British documentary called “The Twin Inside Me” and also published in the New England Journal of Medicine.
Case 4: Lydia Fairchild

Meet Lydia Fairchild from Washington state.

In 2002, Fairchild, a mother of two, with former boyfriend, Jamie Townsend was expecting a third child. Fairchild and Townsend had split up and with no steady work and unable to support herself and the children, she applied for state benefits.

Her world was about to be turned upside down.

Part of the requirement for state benefits including DNA testing on the children and parents.

In December 2002, she received a phone call from the State Prosecutor’s office to come in for the results. This was unusual and it soon became apparent why.

The results revealed that Townsend was the father but they also revealed that Fairchild was not the mother.

A normal DNA test proving a mother-child link would show a 50% match in their DNA patterns, yet Fairchild’s showed no match at all.
Case 4:  Lydia Fairchild

► There was an investigation by the State Prosecutor for illegal surrogacy and welfare fraud.

► Fairchild faced continued questioning, threatened with a lie detector test and ultimately had a summons issued to report to court.

► No one dealing with her case had heard of a chimerism. She could not even get a lawyer as they all considered the DNA evidence irrefutable.

► During the trial, prosecution wanted guardians appointed for each child and based on existing evidence, the judge agreed that Fairchild was not their biological mother.

► Fairchild, now heavily pregnant with her third child, also had the judge order someone be present at the birth to act as a witness and take DNA sample immediately after the birth.

► Those results revealed again, that Fairchild was not the mother and that Townsend was indeed the father of child #3. This was actually great news for Fairchild: Now she could get a lawyer to listen to her case.

► By an extraordinary chance, the prosecutor’s office ran across an article in the New England Journal of Medicine about chimerism......specifically about Karen Keegan (Case 3). Her lawyer demanded that she be screened for chimerism.
Case 4: Lydia Fairchild

► After being approached by her attorney, doctors at the Beth Israel Hospital agreed to investigate Fairchild’s case.

► Just as with Karen Keegan, DNA samples were analyzed from Fairchild’s family members revealing a DNA link between Fairchild and her mother. There was a direct link between the children and their grandmother.

► Fairchild later had a cervical smear in which DNA was tested and found to match that of all three children.

► Fairchild was a twin. The lost or “vanishing” twin had lived on as cells found only in her ovaries.

► Fairchild was her own twin – and the lost twin was actually the biological mother of all of her children.

► Sixteen months later, after enduring the thought of losing her own children, her attorney reflects on the dire consequences of oversight in the testing of DNA. “People go to death row and are released from death row because of DNA tests.”

► As for Keegan and Fairchild – two women separated by thousands of miles but linked by a rare genetic condition, their separate, but bizarre tales, may well have inspired the medical community – and the justice system – to think again about the shortcomings of the “gold standard” DNA test.
Jane Seymour has different colored eyes and twins run in her family (her most recent children are twins.) She was most likely a twin herself and it is almost certain that she is a human-human chimera. Mike (Max) Scherzer, a MLB pitcher for the Detroit Tigers is also most likely a human-human chimera with one dark brown and one light blue eye.
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Questions?