**General Genetics: Genetics and….Special Topics in Genetics Brilakis**  
  
<http://www.drugabuse.gov/publications/topics-in-brief/genetics-addiction>   
from NIDA at HIH:  
  
1. Genetic variation may increase risk of nicotine addiction and lung cancer:  
 A NIDA-supported genome-wide association study recently found that a variant in the gene for a nicotinic receptor subunit doubled the risk for nicotine addiction among smokers (Saccone et al., 2007). A study in Iceland verified this association, finding that this region is also linked to vulnerability to lung cancer and peripheral arterial disease (Thorgeirsson et al., 2008). This is the first evidence of a genetic variation influencing both the likelihood of nicotine addiction and an   
individual's risk for the severe health consequences of tobacco use.  
   
  
2. The COMT gene produces an enzyme that regulates dopamine, a brain chemical involved in schizophrenia. COMT comes in two alleles: "Met" and "Val." Individuals with one or two copies of the "Val" variant have a higher risk of developing symptoms of psychosis and schizophrenic-type disorders if they used cannabis during adolescence.   
  
3. A NIDA-sponsored study of alcohol dependent patients treated with naltrexone found that patients with a specific variant in an opioid receptor gene, Asp40, had a significantly lower rate of relapse (26.1%) than patients with the Asn40 variant (47.9%). In the future, identifying which mu-opioid receptor gene variant a patient possesses may help predict the most effective choice of medication for alcohol addiction.  
  
4. Telomeres:  
 <http://learn.genetics.utah.edu/content/begin/traits/telomeres/>

At the ends of the chromosomes are stretches of DNA called telomeres. Telomeres have been compared with the plastic tips on shoelaces because they prevent chromosome ends from fraying and sticking to each other. Each time a cell divides, the telomeres get shorter. When they get too short, the cell no longer can divide and becomes inactive or "senescent" or dies. This process is associated with aging, cancer and a higher risk of death.   
 Telomeres are made of repeating sequences of TTAGGG on one strand of DNA bound to AATCCC on the other strand. In human blood cells, the length of telomeres ranges from 8,000 base pairs at birth to 3,000 base pairs as people age and as low as 1,500 in elderly people. (An average chromosome has about 150 million base pairs.) Each time a cell divides, an average person loses 30 to 200 base pairs from the ends of that cell's telomeres. Cells normally can divide only about 50 to 70 times, with telomeres getting progressively shorter until the cells become senescent, die or sustain genetic damage that can cause cancer. Telomeres do not shorten with age in tissues such as heart muscle in which cells do not continually divide.  
 After replication, each new matching strand is than the original strand because of the room needed at the end by the primer. It is like someone who paints himself into a corner and cannot paint the corner. An enzyme named telomerase adds bases to the ends of telomeres. In young cells, telomerase keeps telomeres from wearing down too much.   
 As a cell begins to become cancerous, it divides more often, and its telomeres become very short. If its telomeres get too short, the cell may die. It can escape this fate by becoming a cancer cell and activating telomerase, which prevents the telomeres from getting even shorter. Studies have found shortened telomeres in many cancers, including pancreatic, bone, prostate, bladder, lung, kidney, and head and neck. Measuring telomerase levels may be a new way to detect cancer. If scientists can learn how to stop telomerase, they might be able to fight cancer by making cancer cells age and die. In one experiment, researchers blocked telomerase activity in human breast and prostate cancer cells growing in the laboratory, prompting the tumor cells to die. But there are risks. Blocking telomerase could impair fertility, wound healing, and production of blood cells and immune system cells.   
Telomeres and Aging…  
Geneticist Richard Cawthon found shorter telomeres are associated with shorter lives. Among people older than 60, those with shorter telomeres were three times more likely to die from heart disease and eight times more likely to die from infectious disease. While telomere shortening has been linked to the aging process, it is not yet known whether shorter telomeres are just a sign of aging, like gray hair, or actually contribute to aging. If telomerase makes cancer cells immortal, could it prevent normal cells from aging? Could we extend lifespan by preserving or restoring the length of telomeres with telomerase? If so, does that raise a risk the telomerase also will cause cancer? Scientists have been able to use telomerase to make human cells keep dividing far beyond their normal limit in laboratory experiments, and the cells do not become cancerous. So, if telomerase could be used routinely to "immortalize" human cells, it would be theoretically possible to mass produce any human cell for transplantation, including insulin-producing cells to cure diabetes patients, muscle cells for muscular dystrophy, cartilage cells for people with certain kinds of arthritis, and skin cells for people with severe burns and wounds. Efforts to test new drugs and gene therapies also would be helped by an unlimited supply of normal human cells grown in the laboratory.  
 Some long-lived species like humans have telomeres that are much shorter than species like mice, which live only a few years. Nobody yet knows why. But it's evidence that telomeres alone do not dictate lifespan. Cawthon's study found that when people are divided into two groups based on telomere lengths, the half with longer telomeres lives five years longer than those with shorter telomeres. That suggests lifespan could be increased five years by increasing the length of telomeres in people with shorter ones.  
 Some long-lived species like humans have telomeres that are much shorter than species like mice, which live only a few years. Nobody yet knows why. But it's evidence that telomeres alone do not dictate lifespan. Human lifespan has increased considerably since the 1600s, when the average lifespan was 30 years. By 1998, the average U.S. life expectancy was 76. The reasons included sewers,antibiotics, clean water, refrigeration, vaccines and other medical advances that decreased infant mortality, improved diets and better health care. Some scientists believe average life expectancy will continue to increase, although many doubt the average will exceed 90. But a few predict vastly longer lifespans are possible.

5. Genome sizes…just for fun!  
<http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/G/GenomeSizes.html>  
  
6. Artificial Life??  
 In 2008, scientists at the J. Craig Venter Institute (JCVI) reported (in Science 29 February 2008) that they had succeeded in synthesizing a complete bacterial chromosome — containing 582,970 base pairs — starting from single deoxynucleotides. The entire sequence of the genome of Mycoplasma genitalium was already known. Using this information, they synthesized some 10,000 short oligonucleotides, each about 50 bp long, representing the entire genome and then  
assembled these into longer and longer fragments until finally they had made the entire circular genome.   
Could this be placed in the cytoplasm of a living cell?  
The same team showed in the previous year (Science, August 2007) that they could insert an entire chromosome from one species of mycoplasma into the cytoplasm of a related species and, in due course, the recipient lost its own chromosome, destroyed by [restriction enzymes](http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/R/RestrictionEnzymes.html) encoded by the donor chromosome, and began expressing the phenotype of the donor. In short, they had changed one species into another. But the donor chromosome was made by donor bacteria, not synthesized in the laboratory. Still, there should be no serious obstacle to achieving the same genome transplantation with a chemically-synthesized chromosome.

They've done it! The same team reported on 20 May 2010 in the online *Science* Express that they had successfully transplanted a completely synthetic genome based on that of Mycoplasma mycoides into the related species Mycoplasma capricolum. The recipient strain grew well and soon acquired the phenotype of the M. mycoides donor.   
Could this technique be extended to creat novel species?? If so, where does this technology fall within our ethos?  
  
7. HIV:  
HIV is a lentivirus which, like all viruses of this type, attacks the immune system. Lentiviruses are part of a larger group of viruses known as retroviruses. A retrovirus is an [RNA virus](http://en.wikipedia.org/wiki/RNA_virus) that is duplicated in a host cell using a [reverse transcriptase](http://en.wikipedia.org/wiki/Reverse_transcriptase) enzyme to produce DNA from its RNA genome. The DNA is then [incorporated](http://en.wikipedia.org/wiki/Retroviral_integration) into the host's [genome](http://en.wikipedia.org/wiki/Genome) by an [integrase](http://en.wikipedia.org/wiki/Integrase) enzyme. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are [enveloped viruses](http://en.wikipedia.org/wiki/Enveloped_virus) that belong to the viral family *Retroviridae*. The name 'lentivirus' literally means 'slow virus' because they take such a long time to produce any adverse effects in the body.  
  
a. HIV can only enter certain cells, binding to specific receptor proteins. HIV grabs onto cells that have a receptor called CD4. Cells with the CD4 receptor are an important part of the body's immune system. HIV gradually destroys these cells and cripples the immune system.  
It turns out that CD4 isn't the only protein required. Another protein called CCR5 is needed as well. CCR5, called a co-receptor because it works with CD4. It functions sort of like a door that opens to allow HIV to enter the cell.   
Some people who show resistance to HIV have a mutation in the CCR5 gene called CCR5-delta32. The CCR5-delta32 mutation results in a smaller protein that isn't on the outside of the cell anymore. Most forms of HIV cannot infect cells if there is no CCR5 on the surface. People with two copies of the CCR5 delta32 gene (inherited from both parents) are virtually immune to HIV infection. This occurs in about 1% of people. One copy of CCR5-delta32 seems to give some protection against infection, and makes the disease less severe if infection occurs. This is more common, it is found in up to 20% of people.   
It is still dangerous to assume you are completely safe from infection if you have the CCR5-delta32 mutation. Some unusual types of HIV can use other proteins for entering cells. Rarely, there have been people who have two mutant CCR5 genes who have died from AIDS. Also, CCR5 is not the whole story of immunity to HIV infection. Some resistant people have been found who have two perfectly normal copies of CCR5. So other genes yet to be identified also contribute to slowing down HIV infection.   
<http://www.youtube.com/watch?v=34GeUa7RzvY>

Using formulas that estimate how long genetic mutations have been around, researchers have discovered that the mutation dates to the Middle Ages. Why would the mutation stick around so long instead of giving up the ghost? In 1665, the plague (Yersinia pestis bacillium***)*** hit a small village in England called Eyam. The town quarantined itself to keep the Black Death from spreading into the rest of the country. A year later, the plague had burnt itself out but half of the townspeople were dead. Was there something special about the half that lived? In 1996, researchers tracked down descendants of the people of Eyam and looked for any mutations they might have in common to explain this high survival rate. What they found was a mutation called CCR5-delta 32. Smallpox, like HIV, can't infect someone with the CCR5-delta 32 mutation.The fact that the genetic mutation also provided protection against HIV centuries later would just be a coincidence. Other researchers argue that a disease like smallpox that has been around continuously since that time is more likely.

b. Research by Professor Robin Weiss, UCL Infection and Immunity, who worked with colleagues in the US to analyse data from a 25-year study of thousands of Americans of different ethnic backgrounds found a genetic variation which evolved to protect people of African descent against malaria has now been shown to increase their susceptibility to HIV infection by up to 40 per cent. Conversely, the same variation also appears to prolong survival of those infected with HIV by approximately two years. The discovery marks the first genetic risk factor for HIV found only in people of African descent, and sheds light on the differences in genetic makeup that play a crucial role in susceptibility to HIV and AIDS.

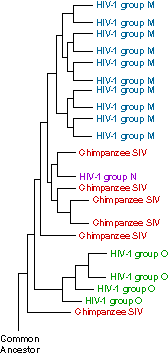
The gene that the research focused on encodes a binding protein found on the surface of cells, called Duffy Antigen Receptor for Chemokines (DARC). The variation of this gene, which is common in people of African descent, means that they do not express DARC on red blood cells. DARC influences the levels of inflammatory and anti-HIV blood factors called chemokines.

Discussing the findings, Professor Weiss said: "The big message here is that something that protected against malaria in the past is now leaving the host more susceptible to HIV.

"In sub-Saharan Africa, the vast majority of people do not express DARC on their red blood cells and previous research has shown that this variation seems to have evolved to protect against a particular form of malaria. However, this protective effect actually leaves those with the variation more susceptible to HIV."

HIV affects 25 million people in sub-Saharan Africa today, an HIV burden greater than any other region of the world. Around 90 per cent of people in Africa carry the genetic variation.

The human immunodeficiency virus is one of the fastest evolving entities known. It reproduces sloppily, accumulating lots of mutations when it copies its genetic material. It also reproduces at a lightning-fast rate. A single virus can produced billions of copies in just one day. HIV evolves so quickly that it evolves right out from under clinical treatments. When a patient begins taking an HIV drug, the drug keeps many of the viruses from reproducing, but some survive because they happen to have a certain level of resistance. Because of HIV's speedy evolution, it responds to selection pressures quickly: viruses that happen to survive the drug are favored, and resistant virus strains evolve within the patient, sometimes in just a few weeks.



HIV is closely related to other viruses including SIVs (simian immunodeficiency viruses), which infect primates, and the more distantly related FIVs (the feline strains), which infect cats. However, primates with SIV and wild cats with FIV don't seem to be harmed by the viruses they carry. If scientists can figure out how non-human primates and wild cats are able to live with these viruses, they may learn how to better treat HIV infections or prevent them altogether. The diagram shows some of the evolutionary history of HIV as we know it today. An ancestral virus (bottom) evolved into strains that infected chimpanzees (SIV). Over time, new strains began to infect humans (HIV).

8. The threat of terrorism has raised the possibility that biological agents could be used as weapons. One of the possible agents is the [variola virus](http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/V/Viruses.html#dsDNA), the cause of smallpox. On October 26, 1977, Ali Maow Maalin came down with smallpox in Somalia. Within a few weeks he was fully recovered. Since that time, no cases of smallpox have been reported anywhere in the world. By May of 1980, the World Health Organization (WHO) felt that it could confidently announce that smallpox had been completely eradicated. The WHO also asked that all countries with any stocks of variola virus in their laboratories either:  
a. destroy them  
b. transfer them to one of two secure laboratories: the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia or a state lab in Koltsovo in Russia.

Although 74 countries did so, the fear remains that some countries may have retained stocks of the virus. Even before the complete eradication of smallpox, routine vaccination against the disease was halted in most Western countries. So today anyone under 30 years of age is fully susceptible and even those older may have lost protection against the disease. Smallpox certainly qualified as one of the greatest scourges of humanity. It regularly killed 25% and sometimes as many as 50% of its victims. Introduced into Europe around the sixth century A.D., smallpox rivaled plague in its ability to decimate entire populations. Introduced into the New World in the sixteenth century, smallpox devastated the native populations and played a far greater role than weaponry in the Spanish Conquest. The date of the appearance of smallpox is not settled. It most likely evolved from a rodent virus between 68,000 and 16,000 years ago.

What should we do now? Return to universal vaccination? Or use the vaccine only for emergency and medical people who might be exposed as they responded to a terrorist attack and those people in a "ring" around any person who comes down with the disease. The argument against universal vaccination is that present vaccines are not 100% safe. There is a small, but definite, risk of serious complications from the vaccine itself, especially in people who have an immunodeficiency.   
  
9. Uncle Mike?  
<http://www.newscientist.com/article/mg21328553.700-gorilla-dna-unlocks-secrets-of-our-species.html>

Kamilah the gorilla had her genome fully sequenced, the last of the great apes to do so. The results highlight key similarities between humans and gorillas, our second closest relatives after chimps. Richard Durbin of the Sanger Institute in Cambridge, UK, led the international team that pieced together the western lowland gorilla genome. The genome contains more than 3 billion pairs of DNA letters - roughly the same as humans - and includes about 21,000 genes.  
 Comparing the gorilla genome with chimpanzee and human genomes sheds some light into the origin of our species. Early analysis suggests that the gorilla lineage splintered off from other great apes about 10 million years ago, some 3 million years before chimps and humans split. It's no surprise, then, that chimps and humans have more in common. The sequences found in 70 per cent of great ape genetic material are more closely related in chimps and humans than in gorillas and either species.  
 Despite the long ago split, the remaining 30 per cent of Kamilah's genome turned out to be more closely related to humans or chimps than those species are to one another, suggesting that genes continued to trickle between the three lineages after they split via gene flow. The most likely explanation is that gorilla ancestors interbred with the ancestors of humans and chimps, much like early modern humans and Neanderthals did.  
  
10. Publish or Perish??  
 Two studies reporting what makes the H5N1 bird flu virus transmissible in mammals should be published fully, with no details left out, say flu experts meeting at the World Health Organisation in Geneva. They say the benefits to public health outweigh the risks of bioterrorism, but they concede that publication should be delayed so scientists can "engage in public communication" aimed at preventing "unnecessary anxiety".  
 The decision to publish comes just a few short weeks after the National Science Advisory Board for Biosecurity (NSABB), the US's top biosecurity panel, asked these virologists not to publish the research in detail. The NSABB worried that bioterrorists would use the information to make dangerous, transmissible H5N1 or that other, less careful researchers would repeat the work and let the virus get away. The researchers themselves have always wanted to publish without restriction, and of the [22 people who met in Geneva](http://www.who.int/influenza/human_animal_interface/list_participants/en/index.html), fully half were leading flu researchers. None of the rest were biosecurity experts concerned with bioterrorism.  
 The Geneva group included public health experts from Indonesia and Vietnam, where people are dying of H5N1 and the virus is actively evolving. The chair of the censorship-favouring US panel was also part of this agreement, which the WHO describes as unanimous. The issue has become a lightning rod for debate because the only thing standing between H5N1 bird flu, which infects birds in half a dozen countries in Asia and in Egypt, and a nasty pandemic is that the [virus is hard for humans to catch](http://www.newscientist.com/article/dn21432-doomsday-flu-decision-time-the-story-so-far.html). But we now know it can it become easily transmissible, in mammals anyway. Last year two labs created versions of the flu that transmits fine in ferrets, the best stand-ins for people. Most worryingly, one of the labs, in Rotterdam, the Netherlands, discovered that [as few as five mutations](http://www.newscientist.com/article/mg21128314.600-five-easy-mutations-to-make-bird-flu-a-lethal-pandemic.html) made H5N1 as catchable as ordinary flu, while remaining as lethal as bird flu is now, and it kills around half the people who get it.   
 The two papers were submitted last year to the journals *Nature* and *Science*. The work was funded by the US National Agency for Allergy and Infectious Disease. US authorities [sounded the alarm](http://www.newscientist.com/article/dn21195-bioterror-fears-could-block-crucial-flu-research.html) over fears that the Rotterdam work, especially, would provide a weapon to bioterrorists.  
 The NSABB met in Washington DC and in December [asked that the work not be published in full](http://www.newscientist.com/article/dn21311-killer-flu-research-to-be-censored.html), keeping the methods used to make the virus, and the mutations that made it nasty, under wraps. The journals said they would accept this, as long as some mechanism could be found to get that information to people who needed it – notably scientists handling H5N1 and public health authorities in countries with the virus, both of whom need to watch for those mutations.  
The information has to be made open so that this research can be done rapidly. Finding a way to make it available, without publishing openly in the journals, was what the flu researchers had been trying to work out in Geneva over the last two days.  
 Should the US funders of the work decide who gets the withheld details? Or the journal publishers? Must the poorer countries at risk from H5N1 depend on American largesse for data vital to protecting themselves, after they supplied the viruses with which the research was done in the first place? The political sensitivity of the issue may have carried more weight in Geneva than it did in Washington.  
 The advantages of keeping scientific details from putative bioterrorists must be weighed against the advantages of working on vaccines in an open environment.