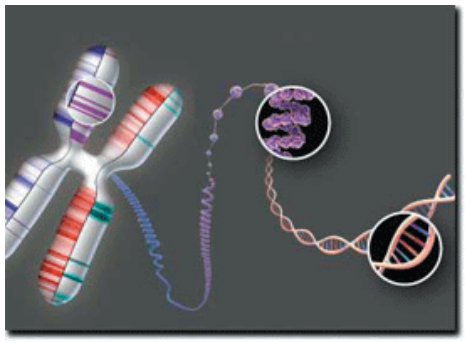
"SNPs and snails and puppy dog tails, and that's what people are made of . . ." A Case Study on Genome Privacy



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Objectives

After completing this case study, you will be able to:

- Define the term *SNP* and list three uses of SNP technology.
- Design an experiment to identify SNPs.
- Describe a potential privacy issue associated with SNP technology.
- Explain the current status of genome privacy laws.
- Apply scientific reasoning skills to an ethical issue in science.
- Write a letter to your United States Representative for/against passage of the Genetic Information Nondiscrimination Act.

Scenario

Various lobbyists and representatives of interest groups will present background information to a mock U.S. House of Representatives Employer-Employee Relations Subcommittee (a subcommittee of the Committee on Education and the Workforce) as they consider voting on the Genetic Information Nondiscrimination Act (an actual bill currently under consideration in the U.S. House).

Follow up Assignment

Write a letter to your U.S. Representative that is either in support of passing or shelving the Genetic Information Nondiscrimination Act. Give substantiated reasons for your position based on your readings and our class discussions. If you are not a U.S. citizen, please write to the local U.S. Representative. Here is where to find contact information for your representative: http://www.house.gov/writerep/.

SNP Overview

> *In April 1999 Terri Seargent went to her doctor with slight breathing difficulties. A simple genetic test confirmed her worst nightmare: she had alpha-1 deficiency, meaning that she might one day succumb to the same respiratory disease that killed her brother. The test probably saved Seargent's life—the condition is treatable if detected early—but when her employer learned of her costly condition, she was fired and lost her health insurance.*

This true story quoted from an article in *Scientific American* ("Pink Slip in Your Genes") illustrates the potential, both good and bad, of our ever-increasing store of genetic information. In the case of Terri Seargent, she had one specific test for one known disorder. SNPs present a new problem, because they have the potential to quickly provide genetic information about many disorders.

What are SNPs? SNP (pronounced "snip") stands for **s**ingle **n**ucleotide **p**olymorphism. Polymorphism refers to the presence of more than one allele of a gene in a population. This allele must be present in more than 1% of the population to distinguish it from a mutation. A SNP is a specific type of allele caused by a small genetic change, or variation, that occurred generations ago within a DNA sequence. The replacement of one single nucleotide with any one of the other three nucleotides resulted in a SNP (see http://las.perkinelmer.com/content/snps/dna-animation.asp). A SNP is, therefore, the simplest kind of polymorphism because it involves only one nucleotide change.

The following is one example of a mutation that may have occurred over evolutionary time, persisted, and resulted in a SNP. Originally, one DNA segment on a chromosome reads GGTAAC. The replacement of the second G with a C created a novel DNA segment that reads GCTAAC. This variation is referred to as a G/C SNP. Each individual in the population inherits a version of the SNP on the chromosome donated from each parent. Therefore, each SNP variant that occurs at a particular site on a chromosome is shared by some fraction of the population.

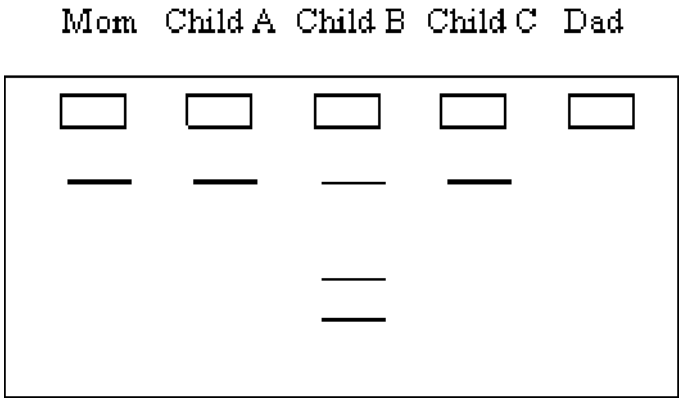
There are probably five to 10 million SNPs in the human genome and it is estimated that about 60,000 of them are found within regions of DNA that code for proteins. Because codons are like words made of three nucleotides (or letters), a single nucleotide change in the DNA sequence of a chromosome alters the codon at that site. The new codon has the potential to direct the cell's machinery to add a different amino acid at this site during protein synthesis. The substituted amino acid may alter either the protein's stability or function. In this manner, SNPs may be responsible for many of the phenotypic differences between humans. The majority of SNPs, however, occur in noncoding regions of the DNA and are not responsible for any protein changes.

How Are SNPs Detected?

After isolation of DNA from an individual, SNPs can be detected by first amplifying DNA in the region of interest using the polymerase chain reaction, or PCR (see http://www.dnalc.org/ddnalc/resources/shockwave/pcranwhole.html). To identify the nucleotide polymorphism, PCR is followed by either hybridization with an allele-specific probe (http://las.perkinelmer.com/content/snps/protocol.asp#hybridization), DNA sequencing (http://www.dnalc.org/ddnalc/resources/shockwave/cycseq.html), or restriction fragment length polymorphism (RFLP) analysis (http://ihome.cuhk.edu.hk/~z045513/virtuallab/animation/rflp.html). Newer methods for identifying SNPs are also available (see http://las.perkinelmer.com/content/snps/protocol.asp and http://www.vetscite.org/issue1/tools/txt_leut_0800.htm).

Study Questions

1. At what position in a codon is a SNP least likely to code for a new amino acid?
2. Explain why we can talk about alleles when analyzing SNPs.
3. To the right is the RFLP analysis of one SNP in a genetically related family. Fill in Dad's most likely RFLP pattern.



How Are SNPs Being Used?

SNPs are being identified that serve as genetic markers for disease. In order to establish a link between a SNP and a specific disease, the genomes of many different individuals need to be scanned for SNPs. Several SNPs are identified within the individual and a SNP profile is constructed. The identified SNPs are also recorded in web-based databases. To determine whether a particular SNP is associated with a disease, the frequency of the SNP pattern found in individuals affected with a disease is compared to the SNP pattern found in unaffected individuals. A SNP may confer disease susceptibility if one pattern is found to be significantly more common in the affected population than in the control group. In some cases, a disease-linked SNP has been identified and a screening test for the disease based on the SNP has been developed. Information about an individual's SNP profile may indicate whether one is at an increased risk, for example, of developing heart disease. The individual may then be able to modify their lifestyle or take medications to prevent the disease rather than waiting for symptoms to occur. However, a SNP profile could also identify other diseases, such as Huntington's, for which there is no effective prevention or treatment. It is important to note that although SNPs may serve as genetic markers for a disease, the majority are not responsible for causing the disease.

It may theoretically become possible to scan one's entire genome for all SNPs. A complete genome SNP profile could indicate a whole range of diseases to which one is predisposed. Currently, the cost of sequencing every individual's genome is prohibitive. However, as Glyn Moody, author of *Digital Code of Life: How Bioinformatics is Revolutionizing Science, Medicine, and Business*, writes, "with a dozen companies racing towards the goal of the sub-$1000 genome, the day when your DNA is sequenced and burnt on to a CD-ROM for roughly the cost of a conventional health checkup is not far off" (*The Guardian*, April 15, 2004).

SNP profiles can be used in medicine beyond identifying disease risk. One hot area in pharmaceutical research is the design of personalized drug treatments based on a patient's SNP profile. SNP information could allow drug therapy to be customized. Individuals always vary in their response to medication both in terms of effectiveness and side effects. SNPs may provide information about the most appropriate drug to prescribe or the optimal dose. One example is the SNP that occurs in the morphine receptor. Individuals homozygous for one SNP allele are known to need much higher levels of morphine-derived pain relieving drugs. Development of a SNP screening test will allow treatment of those individuals with the appropriate dose of morphine.

In addition to medical uses, SNPs are proving useful in mapping the migrations of human populations. SNPs provide information about human evolution and the descent from ancestral populations (see, for example, "Who Were the Phoenicians?" in the October 2004 issue of *National Geographic*, available online at http://magma.nationalgeographic.com/ngm/0410/feature2/index.html).

Challenge Study Questions

1. Explain how a SNP that does not change a protein's sequence can still be associated with a disease.
2. Why do SNPs persist in populations?
3. You are working at a pharmaceutical company developing novel pain medications that bind the morphine receptor. Public databases provide information on the SNP associated with the morphine receptor that affects an individual's response to medication. You have 25 individuals you plan to screen for the receptor-associated SNP and then test for their response to your medication. Which of the SNP detection methods are you most likely to use to screen these individuals for the SNP? (Refer to the section above, "How Are SNPs Detected?") Why?

4. The substitution of a T for an A in the protein coding sequence of the hemoglobin beta chain gene introduced a SNP. This SNP changed the amino acid incorporated into the hemoglobin beta chain, resulting in the disease symptoms of sickle cell anemia. Unaffected individuals have the DNA sequence GAGGAG, a BseR I restriction enzyme site, in their hemoglobin beta chain gene. The T substitution (GTGGAG) eliminates this restriction enzyme site. Explain how you would use this information to design an RFLP screening test for sickle cell anemia. Draw the RFLP gel including results for a carrier, and both unaffected and affected individuals.

Ethical Issues

So, SNPs sound useful. Why are SNPs an ethical issue? As with most things, along with the advantages of our increased knowledge of SNPs and the genome come certain risks. There are privacy issues with genetic information, just as there are with medical records. The easy availability of data from an individual's genome, including SNPs, raises concerns about the possibility of discrimination, stigmatization, loss of insurance, and loss of employment for the individual and their family members. In a study published in 1999 by Dorothy Wertz, over 1,000 U.S. genetics professionals surveyed reported that almost 700 patients had lost their jobs or insurance because of genetic test results even though they had no symptoms. (*Nature Reviews Genetics* 3, 496 (2002); doi:10.1038/nrg854). Terri Seargent's story is not unique.

All of the uses of SNPs outlined above depend upon public databases on the Internet that provide open access not only for scientists, but to anyone who searches. SNPs can be used to identify individuals. Unrelated people differ in about 0.1% of their 3.2 billion nucleotides. Even though there are roughly six billion people on the planet, one single individual can be uniquely defined by only 30 to 80 independent SNP positions. Individuals participating in a research study, for example, may have their SNP profiles posted. Routine blood samples taken during physical exams could also provide DNA for SNP analysis. Inadvertently, an individual's complete SNP profile could be determined, and the potential risk is that this information may be used or shared in a way unintended by the individual.

Concerned scientists have requested that the Senate and House pass laws that protect employees, e.g., laws that would ban employers from using DNA testing in hiring or firing employees. Francis S. Collins, a key player in the Human Genome Project, is one such scientist. In addition to scientists, many national organizations including the National Breast Cancer Coalition and the Council for Responsible Genetics have urged support for additional legislation. In their position paper entitled "Genetic Discrimination," the latter group raises the issue of genetic testing information and life insurance. Lobbyists for the American Council of Life Insurance have already argued that if an individual is known to carry genes linked to an increased risk of cancer, the information should be made available when underwriting insurance policies. One possible result is that high risk individuals may be denied coverage or made to pay higher premiums. Fear of just such an outcome may prevent some individuals from agreeing to testing in the first place. With appropriate genetic test results, physicians are able to monitor high risk individuals early and regularly for signs of cancer or other treatable diseases. If patients are afraid to be tested, their treatment may be less than optimal.

Over the past few years, many proposed bills dealing with genetic privacy and nondiscrimination have failed and successful laws have not received widespread support. Current laws have been criticized because they lack adequate enforcement measures. "There is no federal law on the books to protect [private-sector] employees, because members of Congress have their heads in the sand," according to Joanne Hustead, a policy director at the National Partnership for Women and Families. "Your video rental records are more protected."

One current piece of federal legislation being considered by the U.S. House of Representatives is the Genetic Information Nondiscrimination Act. The Act has been reintroduced a number of times and is currently in committee. The subcommittee assigned this piece of legislation is the Employer-Employee Relations Subcommittee. The entire Act is available on the Web (go to http://thomas.loc.gov/ and search on "Genetic Nondiscrimination." You may also directly contact your U.S. representative to obtain information if you are interested.) The following are key excerpts from the Act:

a. Use of Genetic Information- It shall be an unlawful employment practice for an employer—
    1. to fail or refuse to hire or to discharge any employee, or otherwise to discriminate against any employee with respect to the compensation, terms, conditions, or privileges of employment of the employee, because of genetic information with respect to the employee (or information about a request for or the receipt of genetic services by such employee or family member of such employee); or
    2. to limit, segregate, or classify the employees of the employer in any way that would deprive or tend to deprive any employee of employment opportunities or otherwise adversely affect the status of the employee as an employee, because of genetic information with respect to the employee (or information about a request for or the receipt of genetic services by such employee or family member of such employee).

b. Acquisition of Genetic Information- It shall be an unlawful employment practice for an employer to request, require, or purchase genetic information with respect to an employee or a family member of the employee (or information about a request for the receipt of genetic services by such employee or a family member of such employee) except—
    1. where an employer inadvertently requests or requires family medical history of the employee or family member of the employee;
    2. where—
        A. health or genetic services are offered by the employer, including such services offered as part of a bona fide wellness program;
        B. the employee provides prior, knowing, voluntary, and written authorization;
        C. only the employee (or family member if the family member is receiving genetic services) and the licensed health care professional or board certified genetic counselor involved in providing such services receive individually identifiable information concerning the results of such services; and
        D. any individually identifiable genetic information provided under subparagraph (C) in connection with the services provided under subparagraph (A) is only available for purposes of such services and shall not be disclosed to the employer except in aggregate terms that do not disclose the identity of specific employees;
    3. where an employer requests or requires family medical history from the employee to comply with the certification provisions of section 103 of the Family and Medical Leave Act of 1993 (29 U.S.C. 2613) or such requirements under State family and medical leave laws;
    4. where an employer purchases documents that are commercially and publicly available (including newspapers, magazines, periodicals, and books, but not including medical databases or court records) that include family medical history; or
    5. where the information involved is to be used for genetic monitoring of the biological effects of toxic substances in the workplace, …

Not everyone agrees that more legislation is the answer. Dorothy Wertz, a social scientist who has published widely on ethical issues in genetics, described new laws as "simply Band-Aids on the problem" and wrote that the solution is a national public health system. Others feel that a better solution is to fix flaws in existing legislation rather than develop a separate law applying only to genetic information. Current laws that these groups contend already deal with privacy and genetic information include the American with Disabilities Act (ADA) and the HIPAA privacy act (Health Insurance Portability and Accountability Act of 1996).

To understand this case we need to know about existing laws and their strengths and weaknesses, in particular the ADA and HIPAA. What are the arguments for and against the Genetic Information Nondiscrimination Act? Why has the bill been shelved multiple times? What are appropriate enforcements for the current laws? Should genetic information be private and protected?

Your Role

The class will be divided into the six lobbying groups listed below. Each lobbying group will work together throughout the case study. Use the online resources to research your position. Each group will discuss the Genetic Information Nondiscrimination Act and related issues, and then organize and present the key arguments from your lobbying group's position to the mock House Subcommittee.

Lobbying Groups

- Health insurance companies
- Life insurance companies
- National Breast Cancer Coalition
- EEOC (Equal Employment Opportunity Commission)
- Scientists (academic and industrial/pharmaceutical)
- Genetic counselors and physicians

1) One major argument for not passing new genetic privacy bills such as the Genetic Information Nondiscrimination Act is that current legislation (i.e., HIPAA and the ADA) already provides individuals with protection. Is current legislation sufficient?

National Breast Cancer Coalition:
Is HIPAA sufficient? Go to the HIPAA website http://www.hhs.gov/ocr/hipaa/ and to the National Breast Cancer Coalition website http://www.natlbcc.org. Give a brief overview of HIPAA. Think about arguments from health or life insurance lobbyists (look at their web sites below).

Equal Employment Opportunity Commission:
Is the ADA sufficient? Go to the ADA website http://www.usdoj.gov/crt/ada/adahom1.htm and the *Scientific American* article: "Pink Slip in your Genes." Give a brief overview of the ADA. Think about arguments from health or life insurance lobbyists (look at their web sites below).

Health Insurance Lobbyists:
Go to the American Benefits Council website (http://www.appwp.org) and read "Key issues regarding the Genetic Nondiscrimination Act" (http://www.appwp.org/newsroom/genetic_keyissues.cfm) and "Decoding the Genome, Genetic Predisposition to Disease, and Health Insurance: What Do We Know and Who Do We Share It With?" (http://www.sagecrossroads.net/Default.aspx?tabid=68). Look at the web sites listed for Equal Employment Opportunity Commission and National Breast Cancer Coalition (listed above).

Life Insurance Lobbyists:
Read "Bridging the Gap Between Life Insurer and Consumer in the Genetic Testing Era: The RF Proposal" (http://www.ornl.gov/sci/techresources/Human_Genome/resource/keefer.html) and "Gene Privacy" (http://www.abc.net.au/catalyst/stories/s545820.htm). Go to the American Benefits Council website (http://www.appwp.org). Look at the web sites listed for Equal Employment Opportunity Commission and National Breast Cancer Coalition (listed above).

2) One concern among scientists, physicians, and grass roots organizations such as the Breast Cancer Coalition is that an individual's willingness to participate in a research study or undergo certain tests based on a physician's recommendation may be limited without adequate reassurances there will be no negative repercussions to knowing one's gene status.

Scientists:
Visit the First Genetic Trust web site (http://www.firstgenetic.net/solutions/academic_research.html). Read the article "First Genetic Trust banks on genes" which explains the origins of the company (http://www.nature.com/nbt/journal/v18/n12/full/nbt1200_1236.html). Read: Lin, Z., A.B. Owen, and R.B. Altman. 2004. Genomic research and human subject privacy. *Science* 305:183. http://www.sciencemag.org/cgi/content/full/305/5681/183?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&searchid=1096472024519_6484&stored_search=&FIRSTINDEX=0&volume=305&firstpage=183&fdate=10/1/1995&tdate=9/30/2004. Also check out web sites listed for National Breast Cancer Coalition and Equal Opportunity Employment Commission.

Genetic Counselors & Physicians:
Read the "Council of Responsible Genetics Position Paper on Genetic Testing," (http://www.appwp.org/newsroom/genetic_keyissues.cfm), "Pharmacogenetics to come" (http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v425/n6960/full/425749a_r.html&filetype=&dynoptions) and an article about the situation in Iceland: "Human Genetics: DeCODING Iceland's DNA" (http://www.bioteach.ubc.ca/Bioinformatics/DeCODE/). Also check out web sites listed for National Breast Cancer Coalition and Health Insurance.

Links to Websites

- Site for Genetic Information Nondiscrimination Act: http://thomas.loc.gov/
- Genetic privacy: http://www.ornl.gov/sci/techresources/Human_Genome/elsi/legislat.shtml
- Health Insurance Portability and Accountability Act of 1996: http://www.hhs.gov/ocr/hipaa/
- ADA: http://www.usdoj.gov/crt/ada/adahom1.htm
- Ethics of SNP haplotype mapping: http://www.wellcome.ac.uk/en/genome/thegenome/hg04f002.html
- Iceland (SNP profiles are being created for the entire population): http://www.bioteach.ubc.ca/Bioinformatics/DeCODE/

- National Breast Cancer Coalition:
  http://www.natlbcc.org
- American Benefits Council, Key issues regarding the Genetic Nondiscrimination Act
  http://www.appwp.org/newsroom/genetic_keyissues.cfm
  Covers why a new law may not be required, problems with definitions of terms, issues with enforcement and unlimited liability in courts
- *Scientific American* article: "Pink Slip in your Genes":
  http://www.sciam.com/print_version.cfm?articleID=0005F2E1-3135-1C71-84A9809EC588EF21
- Alternate sites for the article "Pink Slip in Your Genes":
  http://www.mult-sclerosis.org/news/Jan2001/GeneticDiscrimination.html
  http://www.theexperiment.org/articles.php?news_id=1060
- Glyn Moody article:
  http://www.guardian.co.uk/online/story/0,3605,1191683,00.html
- Pharmacogenetics to come:
  http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v425/n6960/full/425749a_r.html&filetype=&dynoptions
- First Genetic Trust—link between collecting patient info and consent and research institutions while protecting patient privacy:
  http://www.firstgenetic.net/solutions/academic_research.html.
  Also see the company backgrounder "First Genetic Trust banks on genes":
  http://www.nature.com/nbt/journal/v18/n12/full/nbt1200_1236.html.
- Decoding the Genome, Genetic Predisposition to Disease, and Health Insurance: What Do We Know and Who Do We Share It With?:
  http://www.sagecrossroads.net/Default.aspx?tabid=68
- Life insurance:
  Keefer, C.M. 1999. Bridging the Gap Between Life Insurer and Consumer in the Genetic Testing Era: The RF Proposal. *Indiana Law Journal* 74(4):1375–1397.
  http://www.ornl.gov/sci/techresources/Human_Genome/resource/keefer.html
  Australian Broadcasting Corporation. 2002. Gene Privacy.
  http://www.abc.net.au/catalyst/stories/s545820.htm
- SNP background:
  http://www.ncbi.nlm.nih.gov/About/primer/snps.html
- Research subject privacy:
  Lin, Z., A.B. Owen, and R.B. Altman. 2004. Genomic research and human subject privacy. *Science* 305:183.
  http://www.sciencemag.org/cgi/content/full/305/5681/183?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&searchid=1096472024519_6484&stored_search=&FIRSTINDEX=0&volume=305&firstpage=183&fdate=10/1/1995&tdate=9/30/2004

Image Credit: Drawing of chromosome to base pairs provided courtesy of The U.S. Department of Energy (DOE), the DOE Joint Genome Institute (JGI), and the Lawrence Berkeley National Laboratory (LBNL) Creative Services Office.