Human Genome Project Information

SNP Fact Sheet

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What are SNPs?

Single nucleotide polymorphisms, or SNPs (pronounced "snips"), are DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered. For example a SNP might change the DNA sequence A**A**GGCTAA to A**T**GGCTAA. For a variation to be considered a SNP, it must occur in at least 1% of the population. SNPs, which make up about 90% of all human genetic variation, occur every 100 to 300 bases along the 3-billion-base human genome. Two of every three SNPs involve the replacement of cytosine (C) with thymine (T). SNPs can occur in coding (gene) and noncoding regions of the genome. Many SNPs have no effect on cell function, but scientists believe others could predispose people to disease or influence their response to a drug.

Although more than 99% of human DNA sequences are the same, variations in DNA sequence can have a major impact on how humans respond to disease; environmental factors such as bacteria, viruses, toxins, and chemicals; and drugs and other therapies. This makes SNPs valuable for biomedical research and for developing pharmaceutical products or medical diagnostics. SNPs are also evolutionarily stable—not changing much from generation to generation—making them easier to follow in population studies.

Scientists believe SNP maps will help them identify the multiple genes associated with complex ailments such as cancer, diabetes, vascular disease, and some forms of mental illness. These associations are difficult to establish with conventional gene-hunting methods because a single altered gene may make only a small contribution to the disease.

Several groups worked to find SNPs and ultimately create SNP maps of the human genome. Among these were the U.S. Human Genome Project (HGP) and a large group of pharmaceutical companies called the SNP Consortium or TSC project. The likelihood of duplication among the groups was small because of the estimated 3 million SNPs, and the potential payoff of a SNP map was high.

In addition to pharmacogenomic, diagnostic, and biomedical research implications, SNP maps are helping to identify thousands of additional markers in the genome, thus simplifying navigation of the much larger genome map generated by HGP researchers.

How can SNPs be used as risk factors in disease development?

SNPs do not cause disease, but they can help determine the likelihood that someone will develop a particular illness. One of the genes associated with Alzheimer's disease, apolipoprotein E or *ApoE*, is a good example of how SNPs affect disease development. *ApoE* contains two SNPs that result in three possible alleles for this gene: E2, E3, and E4. Each allele differs by one DNA base, and the protein product of each gene differs by one amino acid.

Each individual inherits one maternal copy of *ApoE* and one paternal copy of *ApoE*. Research has shown that a person who inherits at least one E4 allele will have a greater chance of developing Alzheimer's disease. Apparently, the change of one amino acid in the E4 protein alters its structure and function enough to make disease development more likely. Inheriting the E2 allele, on the other hand, seems to indicate that a person is less likely to develop Alzheimer's.

Of course, SNPs are not absolute indicators of disease development. Someone who has inherited two E4 alleles may never develop Alzheimer's disease, while another who has inherited two E2 alleles may. *ApoE* is just one gene that has been linked to Alzheimer's. Like most common chronic disorders such as heart disease, diabetes, or cancer, Alzheimer's is a disease that can be caused by variations in several genes. The polygenic nature of these disorders is what makes genetic testing for them so complicated.

The answer to this question is based on information provided by the Genome News Network.

Human Genome Project SNP Mapping Goals

In 1998, as part of their last 5-year plan, the DOE and NIH Human Genome programs established goals to identify and map SNPs. These goals follow.

- Develop technologies for rapid, large-scale identification and scoring of SNPs and other DNA sequence variants.
- Identify common variants in the coding regions of most identified genes.
- Create a SNP map of at least 100,000 markers.
- Develop the intellectual foundations for studies of sequence variation.
- Create public resources of DNA samples and cell lines.

What is The SNP consortium (TSC)?

In April 1999, ten large pharmaceutical companies and the U.K. Wellcome Trust philanthropy announced the establishment of a consortium lead by Arthur L. Holden to find and map 300,000 common SNPs. The goal was to generate a widely accepted, high-quality, extensive, publicly available map using SNPs as markers evenly distributed throughout the human genome. In the end,

many more SNPs (1.8 million total) were discovered. Now that the SNP discovery phase of the TSC project is essentially complete, emphasis has shifted to studying SNPs in populations. Various TSC member laboratories are genotyping a subset of SNPs as part of the Allele Frequency Project. The goal of the TSC allele frequency/genotype project is to determine the frequency of certain SNPs in three major world populations. See the TSC website for more information.

Who are members of the SNP consortium?

The international member companies, which together committed at least $30 million to the consortium's efforts, are APBiotech, AstraZeneca Group PLC, Aventis, Bayer Group AG, Bristol-Myers Squibb Co., F. Hoffmann-La Roche, Glaxo Wellcome PLC, IBM, Motorola, Novartis AG, Pfizer Inc., Searle, and SmithKline Beecham PLC. The Wellcome Trust contributed at least $14 million.

Laboratories funded by these companies to identify SNPs are located at the Whitehead Institute, Sanger Centre, Washington University (St. Louis), and Stanford University. Data management and analysis take place at Cold Spring Harbor Laboratory.

See Consortium Updates:

- News related to The SNP Consortium
- SNP Consortium collaborates with HGP, publishes first progress reports, *2000. Human Genome News*.
- International SNP meeting updates, *2000. Human Genome News*..

Why should private companies fund a publicly accessible genome map?

The SNP consortium views its map as a way to make available an important, precompetitive, high-quality research tool that will spark innovative work throughout the research and industrial communities. The map will be a powerful research tool to enhance the understanding of disease processes and facilitate the discovery and development of safer and more effective medications.

Whose DNA was analyzed to create the consortium's SNP map?

The SNP consortium used DNA resources from a pool of samples obtained from 24 people representing several racial groups. This is a subset of the DNA reference panel for SNP identification collected by the NIH National Human Genome Research Institute. The anonymous, voluntary DNA contributions were made with informed consent specifically for this use.

Are SNP data available to the public?

SNP data were made available through a consortium website at quarterly intervals during the project's first year and at monthly intervals during the second year. This cycle of releases ceased in fall 2001 once the discovery phase was finished, but with recent additions of genotype and allele frequency information, new data were released in fall 2002.

Besides the TSC website, SNP data are also available from the following resources:

- dbSNP database - From the National Center for Biotechnology Information (NCBI).
- HGVbase (Human Genome Variation Database) - A human gene-based polymorphism

database.

For tips on how to use these and other databases, see the Gene Mutation Resources at Gene Gateway, an online guide for learning about genes, proteins, and genetic disorders.

Related Links

SNP Basics

- SNPs: Variations on a Theme - A basic introduction to SNPs from the National Center for Biotechnology Information (NCBI).
- Understanding SNPs and Cancer - An online tutorial from the National Cancer Institute.
- Diseases and Medical Response - An animated tutorial describing how DNA markers are used in medical applications. Part of the Kids Genetics website from GlaxoSmithKline.
- Genome Variations - Questions and answers about genome variation from the Genome News Network.

Articles

- The SNP Consortium Website: Past, Present, and Future 2003. *Nucleic Acids Research* **31**(1), 124-27.
- Introduction to SNPs: Discovery of Markers for Disease 2002. *BioTechniques* (pdf).
- Prospecting for Gold in Genome Gulch 2002. *The Scientist***.**
- Single Nucleotide Polymorphisms: From the Evolutionary Past 2001. *Nature*.
- Single Nucleotide Polymorphisms: . . .To a Future of Genetic Medicine 2001. *Nature*.

Meeting Proceedings and Reports

Fifth International Meeting on Single Nucleotide Polymorphism and Complex Genome Analysis; October 11-14, 2002; Reykjavik, Iceland

Fourth International Meeting on Single Nucleotide Polymorphism and Complex Genome Analysis; October 10-13, 2001; Stockholm, Sweden

Third International Meeting on Single Nucleotide Polymorphism and Complex Genome Analysis September 8-11, 2000; Taos, New Mexico
2000. *Hum. Mutat*. **17**(4), 241-42; 2001. *Eur. J. Hum. Genet.* **9**, 316-18.

Second International Meeting on Single Nucleotide Polymorphism and Complex Genome Analysis; September 17-20, 1999; Schloß Hohenkammer, Germany

Eur. J. Hum. Genet. **8**(2), 154-165 (2000). **Previous Meetings:** 1998. *Science* **281**, 1787-89; 1998. *Nat. Genet*. **20**, 217-18; 1999. *Eur. J. Hum. Genet.* **7**, 98-101.

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