The Human Genome Project and Ectodermal Dysplasia

by

Dr. Angus Clarke, Senior Lecturer in Medical Genetics
University of Wales College of Medicine, Cardiff

There are about three thousand million base pairs of DNA in the human genome, distributed on the 24 different chromosomes visible under the microscope (the twenty-two pairs of autosomes, numbered 1-22, and the two sex chromosomes, X and Y). Buried and dispersed within this massive quantity of DNA are the much smaller sequences of our 30,000 or so genes. These gene sequences control our bodily development and functioning, and when changes occur in the genes they may have far-reaching consequences.

The DNA sequences are copied at every cell division, so that each cell in the body contains a complete set of genes. Alterations in the sequence can easily occur as the DNA is copied - either within the tissues of an individual or in the formation of their egg or sperm cells. These alterations (mutations) may be harmless and without any effects, or they may lead to physical differences for the individual. These can either be harmful differences or, just occasionally, positive enhancements that will be favoured by natural selection. A mutation that occurs within a person's tissues can cause a problem in the cells carrying the change, and may sometimes lead on to cause a cancer. When a mutation occurs in the egg or sperm it is more likely to result in an inherited disorder that may manifest in several parts of the body. If a mutation impairs the function of a gene required for correct formation of the ectodermal structures (hair, teeth, nails and sweat glands), then the affected individual is likely to have an ectodermal dysplasia.

In June of 2000, it was announced that the Human Genome Project (HGP) had completed its 'working draft' of the human gene sequence. Only about a quarter of the sequence was finished - checked to 99.99% accuracy, with less than one error in every 10,000 bases - and a less accurate sequence was available on most of the rest of the genome, although with some gaps. The timing of this announcement was somewhat arbitrary, and was perhaps triggered by the rivalry between the HGP and some commercial competitors eager to patent gene sequences and to exploit their commercial applications, but it represented a very real achievement.

A further milestone has been achieved just this past week - the publication of two competing (but not very different) versions of the complete Human Genome Project. One version has been produced publicly, the other by a private (commercial) group. The release of the data accumulated by these teams - the nearly complete human DNA sequence - means that researchers can now identify most human genes, although there is still some uncertainty as to precisely how many human genes there are. The HGP has transformed the way that much medical research is undertaken. Whereas the search for a gene of potential medical importance used to be slow and laborious, and involved much repetitive laboratory work, it is now possible to approach many research questions by

interacting with computers - 'dry' research instead of 'wet'. Laboratory research is still required but for different purposes - e.g. will this change in that gene alter the quantity or activity of the protein it produces? is this bit of the gene required for its effect on the development of that structure or to prevent that disease?

Many other questions can be approached through the interrogation of computer databases - often using data that have been generated elsewhere and are available publicly over the internet. Thus, one might compare a human DNA sequence with the sequences of corresponding genes in the mouse, fruit fly, brewer's yeast or other organisms. The identification of stretches of DNA sequence that have been largely conserved through evolution may point to the most crucial areas of the corresponding protein. One may use computer programs to predict the likely structure of the protein, and this will often give important insights into its function (if that is not known) and its likely location within the cell.

How important will these developments be for the ectodermal dysplasias? It is likely to lead to the identification of many other genes involved in the less common types of ED. This in itself will help scientists to understand the development of skin and the various ectodermal structures. Experimental work on mice and other organisms may then result in a more detailed understanding of how the various genes work together to achieve normal development. Gene-based therapy, however, is unlikely to be possible for the EDs for many years because the production of ectodermal structures (hair root bulbs, sweat glands, teeth etc) has largely finished by the time of birth - so there is very little scope for treatment. This situation may change, of course, if stem cell research makes it possible to generate new tissues from the individual's own cells that would not risk rejection by the body's immune system. But that must be many years away. And it begs the question of how many people with ED would want to undergo experimental treatments for uncertain benefits. This will depend in part upon how severely affected a person is by their condition - and each person will have to decide that for themselves.

This article was first published in our newsletter (Volume 1 Issue 11 - March 2001).