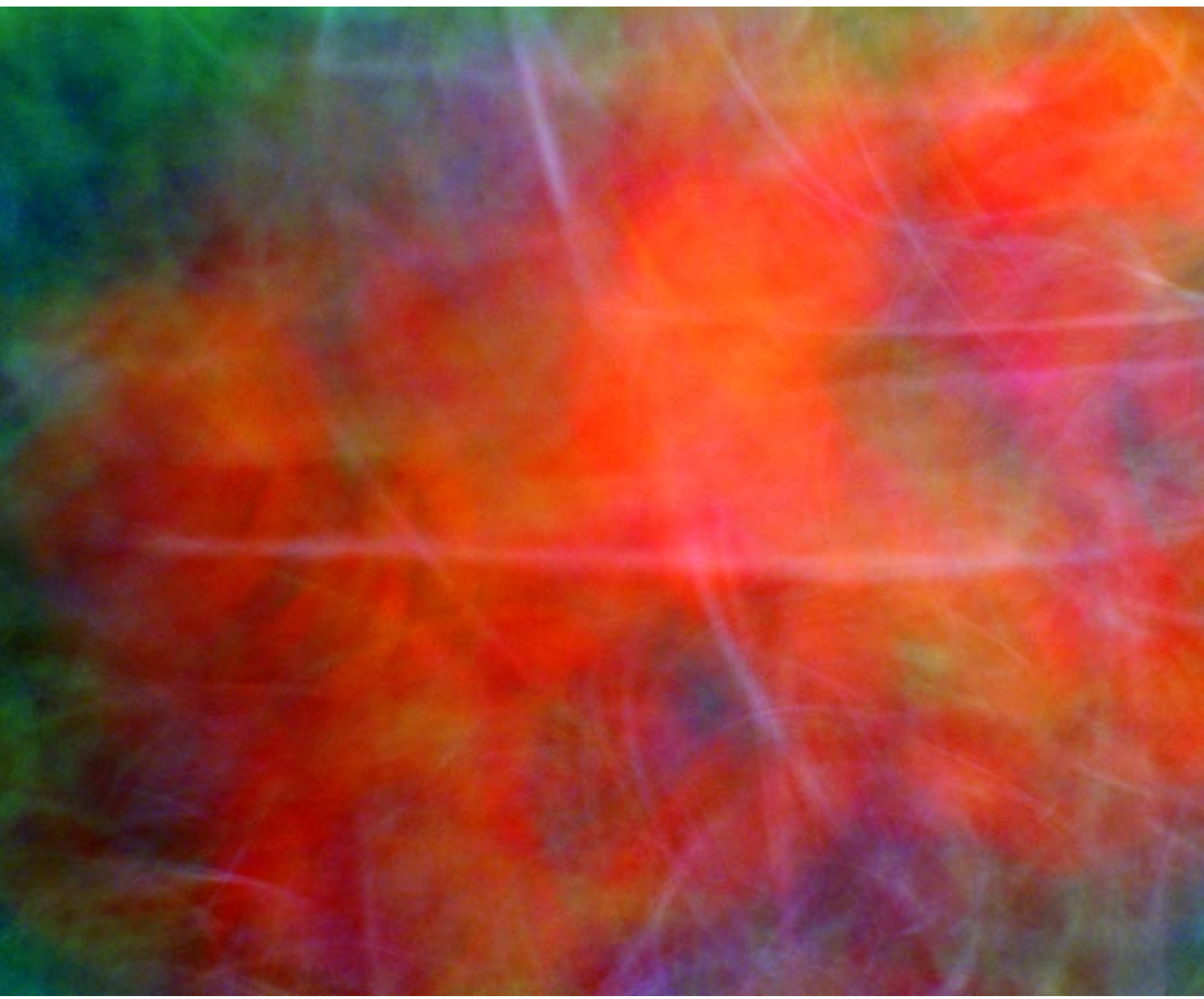
Alpaca Genome Project



The length of Route 66, which starts in Chicago and ends in Los Angeles, represents the alpaca genome. Now imagine you could cut Route 66 up into a thousand overlapping pieces and shake them up. How would you go about putting the map back together?

By Patricia Craven, Ph.D., President, Alpaca Research Foundation

Dr. Warren E. Johnson and his colleagues at the Laboratory of Genomic Diversity, National Cancer Institute, National Institutes of Health, in Frederick, Maryland are hard at work mapping the alpaca genome. This work is being funded by the Alpaca Research Foundation (ARF) and is a joint project of the Morris Animal Foundation and ARF. The work began in September of 2002 and is scheduled for completion in September of 2005. This article will give you some idea of what the goals of the project are and how far along we are in reaching those goals.

Up until the mid 1980's, identification of a gene that is responsible for causing disease could only be accomplished by first identifying the underlying cause of the disease, characterizing the deficient protein or enzyme, and then isolating the gene. With the advent of modern molecular genetics, it is now possible to predict the presence of a gene responsible for a disease without having prior knowledge of the mechanism of the disease or the protein responsible. This is possible through a process called genome mapping.

The genome contains all of the genes for a particular organism. Genes are arranged in a linear fashion along the genome much like cities and towns are positioned along the length of a highway. Fortunately, for gene mappers, the genome also contains a large number of markers that are interspersed between the genes or actually are part of a gene. Imagine a road map of the United States. The single length of Route 66, which starts in Chicago and ends in Los Angeles, represents the alpaca genome. The cities and towns along the highway represent markers. Now imagine you could cut Route 66 up into a thousand overlapping pieces and shake them up.

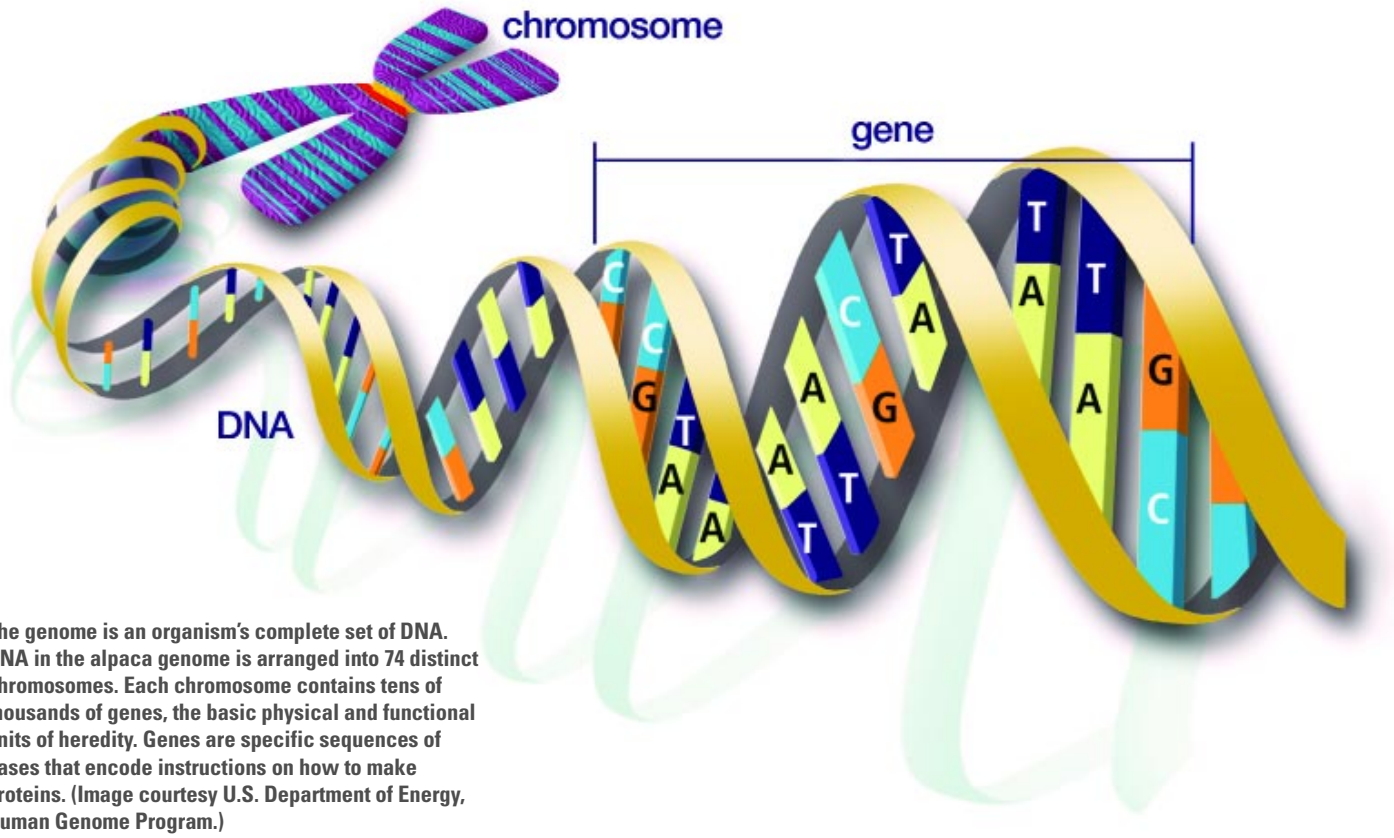
Putting the Pieces Together

How would you go about putting the map back together? The principle is simple. The closer two cities are to each other on the map the more likely they are to appear on the same overlapping fragment of highway. In an analogous way, Dr. Johnson and his colleagues have cut up the alpaca genome into thousands of overlapping fragments by controlled irradiation of a cell line, which they grew from the skin of a pedigreed male alpaca.

They then fused the fragments of alpaca DNA into hamster cells. As the hamster cells grow and divide, the alpaca DNA fragments are also reproduced. The lab has isolated 220 distinct hamster cell lines, each of which is now growing and manufacturing large quantities of alpaca DNA fragments. While they were conducting the irradiation and hamster cell fusions, Dr. Johnson and his colleagues identified over 800 type II markers to be placed on the DNA fragments. The majority of these are dinucleotide and tetranucleotide repeats. Type II markers occur in many different forms and thus are useful for paternity testing and linkage analysis in families. In addition, approximately 100 Type I conserved mammalian markers have been identified for placement on the DNA fragments.

Additional type I markers will be obtained by screening two alpaca DNA libraries, which are currently under construction. Type I markers do not vary in form and can not be used for either paternity testing or linkage analysis. Instead Type I markers, being located on the genes themselves, can help investigators obtain very specific information about the identity of the gene involved in transmitting a specific trait.

Much of the coming year will be spent placing markers on the DNA fragments that are being produced by the hamster cell lines in culture. Once it is determined which markers are on each fragment of the alpaca genome, the data will be fed into a computer that uses highly automated programs to place the DNA fragments in their proper sequence, based on the principle that the closer two markers are to each other on the map, the more likely they are to appear on the same overlapping fragment of DNA. *continued*



The genome is an organism's complete set of DNA. DNA in the alpaca genome is arranged into 74 distinct chromosomes. Each chromosome contains tens of thousands of genes, the basic physical and functional units of heredity. Genes are specific sequences of bases that encode instructions on how to make proteins. (Image courtesy U.S. Department of Energy, Human Genome Program.)

Assembly of the map is scheduled to take place in 2005. (However, mapping the alpaca genome is only one half of the equation. Dr. Johnson and his colleagues welcome input from investigators and members of the alpaca community, interested in developing markers that will be useful for identifying inheritable defects or important traits in alpacas. Possibilities include choanal atresia, angular limb deformities, wryface, polydactyly, brachygnathia, cleft palate, deafness, ventricular septal defect, testicular hypoplasia, ovarian hypoplasia, juvenile lymphosarcoma, and immunodeficiency syndrome.)

Collection of DNA

For a disorder or trait to be amenable to genetic testing, it must first be determined that it is caused by a single gene and is inherited in a predictable pattern. This can be accomplished through breeding trials and through voluntary and anonymous contributions of blood or tissue from alpacas affected by an inherited disease and their families. [Indeed, now is the time to begin planning for the availability of the map by conducting breeding trials and developing pedigrees that trace the pattern of inheritance of traits of interest. The tools will be soon be available for genetic testing in alpacas. The accumulation of a sufficient number of DNA samples for testing is usually the rate limiting step in any linkage analysis.]

Once a sufficient number of DNA samples have been collected, highly automated genome scanning will be used to determine whether the inheritance of a particular marker is associated with the inheritance of a particular trait. The closer a gene is to a marker the more likely it is that the gene and the marker will be passed on together to the offspring, a phenomenon scientists call linkage. Therefore, genes of interest, such as those that cause disease, can be tracked by following the inheritance of the marker rather than the gene itself.

It is particularly valuable in the alpaca because no genes of interest have yet been identified. By selecting those markers which always occur when the disease is present and eliminating those markers which do not always occur in affected individuals, we can develop linkage tests which predict the presence of abnormal genes in phenotypically normal alpacas. [With the availability of a genome map for the alpaca and the placement of a large number of markers, evenly spaced along that map the location of genes of interest on the map can be further refined by looking at the frequency with which a marker is inherited, along with a particular disease or trait. Eventually, a comparison with genome maps from other species will lead to the identification of a "candidate gene." Once a candidate gene is identified and the protein it produces is known, unequivocal tests for the occurrence of that gene in unrelated alpacas can be developed.

The Alpaca Research Foundation, Inc. (ARF) is a non-profit corporation chartered with oversight of alpaca research funding. ARF works in conjunction with Morris Animal Foundation to fund peer-reviewed, humane health care studies of the alpaca. For further information about ARF, please contact Dr. Patricia Craven at alpacone@mail.microserve.net or (724) 397-9211.