

THE *PROGRESS* REPORT



Volume 13

Spring/Summer 2004

Welcome to another edition of the *PROGRESS* Report, a newsletter to update *PROGRESS* study participants about our research. As you know, *PROGRESS* is a study of prostate cancer in families. The goal of the study is to find the genes that explain why prostate cancer runs in some families. By discovering the genetic causes of the disease, we hope to find better ways to detect, treat, and even prevent prostate cancer. We appreciate your ongoing help with the study and hope you enjoy this edition of the newsletter.

New Findings Published from *PROGRESS*

Our last newsletter reported on the completed genome scan of *PROGRESS* families. (A genome scan is a technique used to find disease genes by looking for patterns of inheritance at many different markers, or “stop signs,” along the genome; this allows us to see whether or not individuals with prostate cancer share the same marker patterns.) Our results highlighted several areas of the genome that could harbor hereditary prostate cancer genes.



Published in the same journal issue were seven other hereditary prostate cancer genome scan papers from research groups around the world. Each of the eight scans highlighted different regions of the genome, with very few overlapping results. This is strong evidence that there are likely to be several genes that cause prostate cancer to occur in families. The latest research report published from *PROGRESS* focuses on a single region on chromosome 7 that was associated with prostate cancer in our genomic scan overall, and in particular in a subset of families.

We identified our strongest finding on chromosome 7 by looking at a subgroup of the *PROGRESS* families reporting Jewish heritage. This approach of looking at groups of similar families has proven to be very helpful in locating other disease genes, like the genes for inherited breast cancer (called BRCA1 and BRCA2). The families who enrolled in *PROGRESS* are from different

backgrounds and from all across North America. Because the families are so different (i.e., heterogeneous), it’s possible that there is more than one gene responsible for prostate cancer in these families. By sorting families into groups with similar characteristics (i.e., homogeneous), we hope to increase our ability to find the disease genes. Finding a gene using linkage analysis is a little like tuning in a radio station – once we decrease the noise or static the signal gets stronger. Thus, by focusing on a more similar or homogeneous subset of families we may be able to reduce the noise and thereby pick-up important signals highlighting the location of potential prostate cancer genes. We have analyzed other subgroups of *PROGRESS* families in the past, most notably according to the presence of other cancers within a family. Such an approach helped to find our linkage result on chromosome 1p in families with both prostate cancer and brain cancer.

For our latest result on chromosome 7 we looked at a subset of families who reported their religion or ethnicity as Jewish and who reported that their parents or grandparents came from Central or Eastern Europe. We decided to focus on this subgroup because there is a specific and well-studied population of Jewish people called “Ashkenazi” whose ancestors lived in Europe many years ago. Because of their genetic isolation in the past, due to geography and marriage patterns, Ashkenazi Jewish families may have a more similar genetic profile to each other than would an unselected (more heterogeneous) group of families. We do not know for sure which families in *PROGRESS* are descended from the Ashkenazi Jewish population, but we tried to identify families likely to be Ashkenazi based on reported religion, ethnicity, and country of origin. After applying these criteria, a small group of 17 families remained. (Continued on next page.)

With such a small number of Jewish families, it could be difficult to get a strong result. To improve our ability to detect a genetic signal, we worked with researchers at the Johns Hopkins University (JHU) in Baltimore, MD who have been conducting a family study of prostate cancer similar to *PROGRESS* and had identified a small group of 19 Ashkenazi Jewish families. By combining our efforts, we were able to increase the number of families we could study and had more power to detect an association. Together, there are 36 families in the *PROGRESS* and JHU collections who reported Jewish ancestry and originated from Central or Eastern Europe.

With the combined data on these 36 families, we re-analyzed the genome scan data. We use a technique called “linkage analysis” to determine whether a DNA marker and the disease (prostate cancer) are inherited together more frequently than would be expected by chance alone. The genome scan analysis highlighted a region on chromosome 7. We found eleven sequential genetic markers with positive signals, indicating this part of the chromosome could harbor an inherited mutation in a gene. If we repeated the experiment 1,000 times, we would expect to get a result this strong only six times by chance, a statistic called a p-value.

The importance of this result is not limited to Jewish families, even though that is the group where we first found a signal. Looking in Jewish families may help to “tune in” a weak signal, but the gene identified could be

relevant for non-Jewish families. We know this from the research already conducted in breast cancer. The breast cancer gene BRCA2 was initially identified by a linkage signal found in a subset of families with both male and female breast cancer. (Yes, males can get breast cancer, though it is rare.) By looking in this rare subgroup, the genetic signal for hereditary breast cancer became stronger and a gene with mutations that cause breast cancer was later identified in that area of the genome. Once the BRCA2 gene was identified, mutations in that gene were found to account for breast cancer cases in many families without cases of male breast cancer. Based on that experience, we know that our prostate cancer result in Jewish families could be very important for non-Jewish families too.



The next step in this process of gene discovery is to narrow down the region we have identified and ultimately to find the specific gene responsible for the disease. Within the area we have identified, there are up to two hundred genes depending on how the region is defined. The lab scientists here at the Fred Hutchinson are working very hard to pinpoint which of those genes could harbor a disease-causing mutation(s). We are also working with other researchers in the ICPCG (International Consortium for Prostate Cancer Genetics) to analyze additional Jewish families with prostate cancer. The more families we have, the more genetic information we will gain to help narrow the region and pinpoint the gene. We are hopeful that with further work, we will be successful in our search. As always, we will keep you updated as our research develops.

Recently Published Results from *PROGRESS*

Here's where the recent *PROGRESS* papers were published.

- Genome scan of 254 *PROGRESS* families published in the journal *Prostate* (57: 309-319, 2003)
- Chromosome 7 finding in Jewish families published in *Proceedings of the National Academy of Sciences* (101: 1939-1944, 2004)



If you would like a copy of these or any of our other papers, please call our toll-free number **1-800-777-3035** and we will gladly mail them to you.

The Basics: A Refresher on Genetics

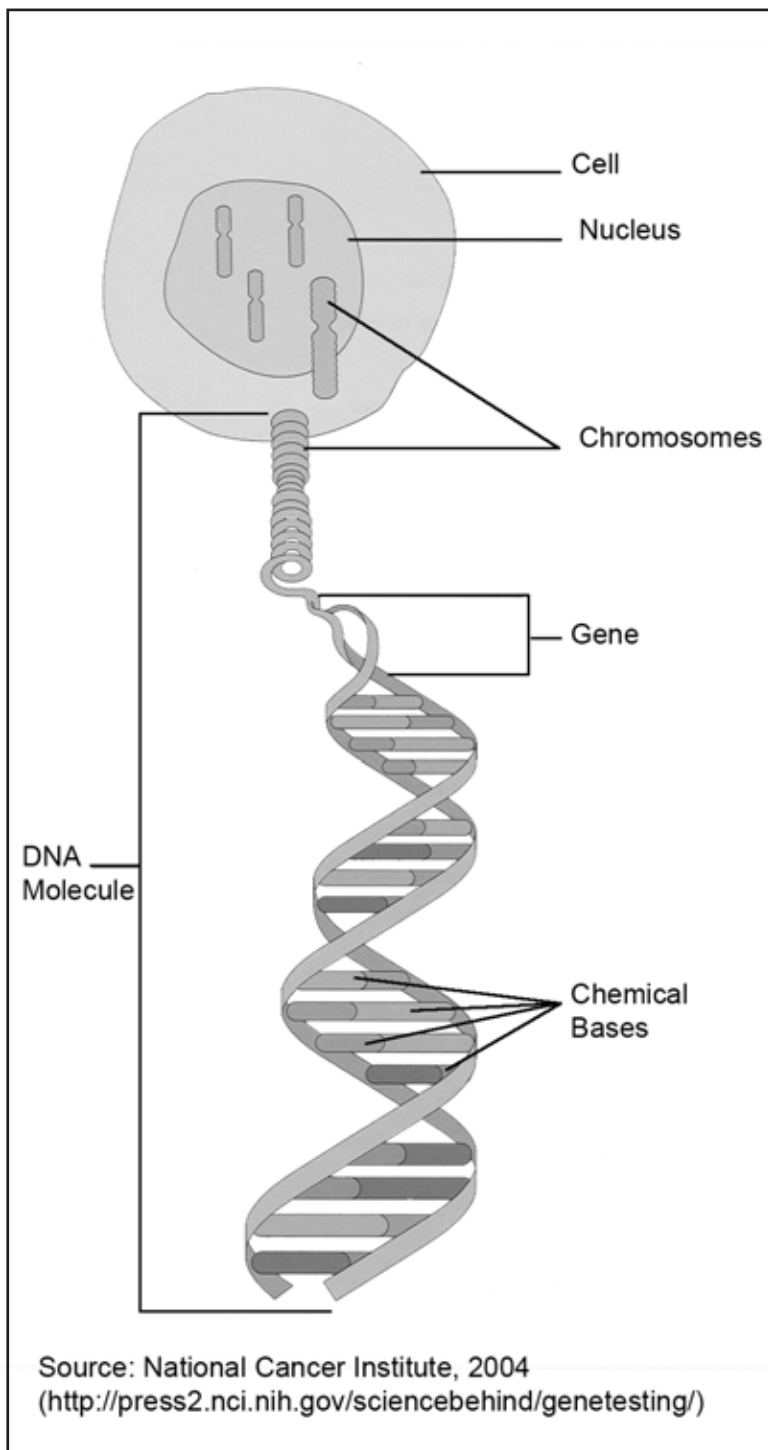
What is a chromosome? What is DNA? What are we talking about? Though our past newsletters have included some genetic basics, here is another explanation of the science and terminology behind genetic research on prostate cancer.

Your body is made up of billions of cells. Inside the nucleus of these cells are 46 chromosomes, arranged in 23 pairs. Chromosomes are long, twisted strands of DNA that contain all the instructions your cells need to keep your body functioning. DNA is made of millions of chemical building blocks called bases. There are only four different bases in DNA but the order in which the bases occur determines the information available, like letters of the alphabet can combine to form words and sentences.

At birth, every cell in your body contains the same DNA. Your DNA “code” is unique – no other person shares the same exact sequence of bases (except if you have an identical twin.) Genes are portions of DNA that contain instructions for making a specific product, usually a protein. The “human genome” is all the genetic material in a human – the full set of instructions coded in the DNA of all 23 pairs of chromosomes. Scientists estimate that the human genome contains between 30,000 and 35,000 genes, all coiled up in the 23 pairs of chromosomes in every nucleus of each cell in your body. Although all cells in your body contain the full DNA sequence, each cell uses only some of the genes in the “instruction book.” A normal cell will activate, or turn on, only the genes it needs and the other genes are turned off, or suppressed.

It has been said that “all cancer is genetic.” All cancer results from cells that divide over and over. Scientists think this uncontrolled growth occurs because one or more genes are not working the way they should. Genes can be turned on when they should be turned off or turned off when they should be on. Sometimes the DNA instructions are jumbled and the gene does not have the right “recipe” for the protein it should produce.

The genes that cause prostate cancer are not yet known – that is why we are conducting the *PROGRESS* Study. We evaluate the DNA from men who have the disease and from family members who don’t have the disease. We are slowly learning what areas on the chromosomes are associated with prostate cancer in families (see illustration on next page). Now we are studying these regions in more detail to see exactly what DNA sequence or genes are at that location.



Other Genes and Loci

Many different teams from around the world have been working to figure out the puzzle of hereditary prostate cancer. There have been several findings of potential hereditary prostate cancer genes in addition to our findings on chromosome 7. Here is a brief summary of those findings.

Two genes have been identified as “candidate genes” based on linkage analysis results. Though the genes have been pinpointed, there is still debate about how frequently mutations in these two genes are the cause of prostate cancer.

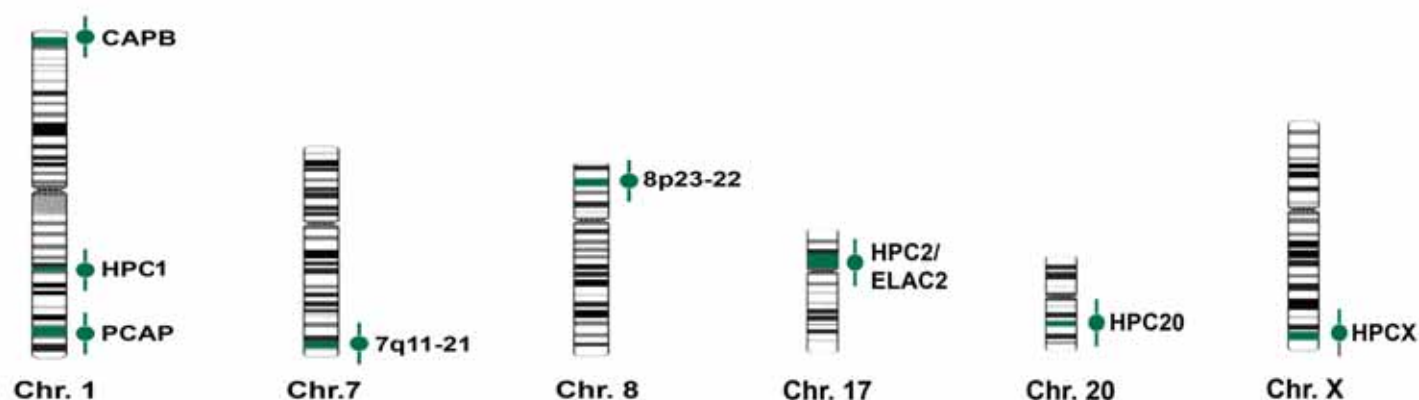
- HPC1, located on chromosome 1q, identified in 1996, Candidate gene: “RNASEL”
- HPC2, located on chromosome 17q, identified in 2000, Candidate gene: “ELAC2”

There are several other locations on the genome that have been identified in much the same way as our result on chromosome 7. These regions are reported to be

associated with hereditary prostate cancer, but no specific gene has yet been identified. Scientists are still working to narrow the region for these results.

- HPCX, located at chromosome Xq27-28, reported in 1998.
- PCAP, located at chromosome 1q42.2-43, reported in 1998.
- CAPB, located at chromosome 1p36, reported in 1999.
- HPC20, located at chromosome 20q13, reported in 2000.
- Chromosome 8p22-23, reported several times, possible candidate gene: “MSR1”

In addition to these genes, there are several other parts of the genome reported to be associated with prostate cancer based on results from our genome scan and others. Any of these regions could contain a susceptibility gene for prostate cancer. Further research is continuing into all these regions in hopes of finding the cause(s) for inherited prostate cancer.



On the Move!

The *PROGRESS* staff and the entire Fred Hutchinson Division of Public Health Sciences are now settled into a new location. We are located in a new building on the main Cancer Center campus in Seattle, near the south end of Lake Union. Our new address is:

PROGRESS

Fred Hutchinson Cancer Research Center
P.O. Box 19024, Mailstop M4-A402
Seattle, WA 98109-1024

As always, you can reach us by telephone (toll-free) at 1-800-777-3035.
Please feel free to call us if you have questions or to report any family updates.

