Greetings

Welcome to the 19th edition of The Progress Report, a newsletter for participants in the Prostate Cancer Genetic Research Study or PROGRESS. The goal of the newsletter is to keep in touch with you and to provide updates on our latest research findings. Our hope is that you will find it both informative and helpful. We really appreciate your ongoing participation and help with the study. If you have any questions about this newsletter or your participation, please call us toll-free at 1-800-777-3035. We are always pleased to hear from you.

Study Updates

Next Generation Sequencing Projects Underway

The findings from our recent genome-wide single nucleotide polymorphism (SNP, a type of genetic marker) linkage analysis of 96 PROGRESS families with both prostate cancer and colon cancer have been published (Fitzgerald et al., Eur J Hum Genet 2010; 18: 1141). In the overall analyses we observed a suggestive signal or linkage peak on three chromosomes: 11q25, 15q11-14 and 18q21. Each of these linkage peaks points to a particular region on a chromosome that may harbor a causative gene and mutation for prostate cancer in a sub-group of families. Stronger evidence for linkage was achieved when only prostate cancer families with at least two members with colon cancer were analyzed, a total of 27 families. In this subset of families the signal on chromosome 15q11-14 became more significant.

A similar region on chromosome 15 produced one of the strongest signals in our genome-wide SNP linkage scan of approximately 6,000 genetic markers (Stanford et al., Hum Mol Genet 2009; 18:1839). When we looked at all of the families together, a total of 301 families, we found evidence of linkage peaks at chromosomes 7q21, 8q22 and 15q13-14. Among families in which the men with prostate cancer had an average age at prostate cancer diagnosis of less than 65 years, the signal at chromosome 15q13-14 was even stronger. This region has also been identified in earlier prostate cancer linkage studies, including a meta-analysis of data from 1,233 families conducted by the International Consortium for Prostate Cancer Genetics (ICPCG).

These consistent findings indicate that this segment on the long arm of chromosome 15 is an important candidate region that needs further follow-up.
To this end, we recently embarked upon an exciting new project to investigate chromosome 15q13-14 using the latest genetic technology, next generation sequencing (NGS; see sidebar). For this project, we are including nine PROGRESS families with strong evidence of linkage to chromosome 15q. In addition, we are including five families from the ICPCG that also show evidence of linkage to 15q13-14. At least three individuals from each family have been selected for next generation sequencing. The region on chromosome 15q13-14 is large, encompassing over 1,000,000 bases of DNA, and the sequencing will take several months to complete, after which analyses of the data will begin. We are excited about the level of detail and extensive genetic data provided by NGS and we are looking forward to seeing the results from this project. As always we will keep you up-to-date on our findings once they become available.

Next Generation Sequencing

DNA is made up of 4 chemical bases or nucleotides: Adenine (A), Guanine (G), Cytosine (C), and Thymine (T). These bases join together via a hydrogen bond to form base-pairs. Adenine always bonds with Thymine (A to T) and Cytosine always bonds with Guanine (C to G) and the 2 strands of DNA to which they belong, wind around each other to form the classic double-helix shape of DNA (See Figure 1).

Our earlier SNP linkage scan looked for changes in particular bases that were spaced evenly along the length of the entire genome (all 23 chromosomes). Next Generation Sequencing (NGS) involves examining all of the base pairs across the entire genome (called whole-genome sequencing), across a defined segment of the genome (targeted sequencing), or across all the coding regions of the genome (called whole-exome sequencing; see below). For targeted sequencing such as our project on chromosome 15q, the region under investigation can encompass several genes.

NGS is a complex process consisting of multiple steps. DNA from an individual is chopped up into small fragments (~200 bases), which are attached to a glass slide, or array and placed onto a sequencing machine. The arrays are then washed thousands of times with different chemicals that react with the DNA bases to produce flashes of light. For example, the first wash would be with a chemical that reacts with the Adenine (A) base and flashes blue, the second wash would be with a chemical that reacts with the Thymine (T) base and flashes red, and so on. A tool similar to a digital camera takes an image of the flashes after each wash, thereby recording the DNA sequence for each ~200 base fragment. The information from the sequencing machine is transferred to a computer where the analysis begins. Each small DNA sequence is lined up against a “reference” sequence taken from the Human Genome Project. The Human Genome Project sequenced the entire human genome and has made this information available to scientific researchers. Any bases that don’t match the “reference” sequence are identified and investigated further as these mis-matches may be genetic mutations or changes that cause disease.
Whole-Exome Sequencing Pilot Project

Genes are made up of coding and non-coding regions, known respectively as exons and introns. The coding regions – exons – are the blue-prints for building proteins, which are responsible for just about every process that goes on in your body. Mutations or genetic changes that occur in exons can cause dramatic changes in the way a protein is made. This in turn can affect the way a protein works in the body, including causing disease.

Whole-exome sequencing (WES) involves reading all of the base pairs within all of the exons (known collectively as the exome) across a person's entire genome (see Figure 2). The exome represents only about 1.5% of the whole genome, however there are around 180,000 exons altogether, which add up to almost 30 million bases. We were recently selected as part of a competitive process for a WES pilot project by the Center for Inherited Disease Research (CIDR). CIDR also previously performed the genotyping for the genome-wide SNP linkage scan of PROGRESS families that was completed in 2007.

For the WES project we selected 19 families with the highest number of men diagnosed with a more clinically advanced form of the disease and/or the highest number of men with an earlier age at diagnosis of prostate cancer. By studying families with evidence of more aggressive or early onset disease, we hope to discover some of the causative genes and mutations responsible for hereditary prostate cancer. We would then investigate these genetic changes further in the remaining PROGRESS families. Approximately 90 family members are being sequenced for this WES project. Due to the large amount of data generated, these analyses will take some time to complete. As always we will keep you up-to-date on our findings once they become available.

Health Status Updates

In order to keep family and clinical records up to date and to maximize the accuracy and power of our study analyses, it is very important that you keep us informed about any changes in your current health status. We would particularly like to know of any new diagnosis of prostate cancer or any other type of cancer in your family. Such information would be very useful for the continuing efforts of the study to try and identify the genetic mutations that contribute to development of hereditary prostate cancer. You can reach us via any of the methods listed in the “Contact Information” section below. Your help is always very much appreciated and we would like to thank you for your ongoing participation in the PROGRESS study.

Although we are unable to provide clinical advice to study participants, we can pass on some useful toll-free information lines and websites that contain up-to-date information and access to expert advice regarding the latest screening guidelines and treatment options for prostate cancer:

National Cancer Institute, Cancer Information Service
1-800-422-6237
http://www.cancer.gov/cancertopics/types/prostate

American Cancer Society
1-800-227-2345
http://www.cancer.org/index

Prostate Cancer Foundation
1-800-757-2873
http://www.pcf.org/site/c.LeJRIROrEpH/b.5699537/k.BEF4/Home.html
**Study Staff**

Investigator: Janet Stanford, PhD  
Study Manager: Laura McIntosh, PhD  
Sample Manager: Suzanne Kolb, MPH  
Post-Doctoral Fellow: Liesel FitzGerald, PhD  
Program Assistant: Jack Kindred

**Contact Information**

Mailing Address:  
Fred Hutchinson Research Center  
P.O. Box 19024, M4-A402  
Seattle, WA 98109-1024

Toll-Free Number:  
1-800-777-3035

Email:  
progress@fhcrc.org  

Website: http://www.fhcrc.org/phs/progress_study/index.html

If you would like copies of our earlier newsletters or for additional information regarding the study, including a list of published study-related articles, please visit our website: http://www.fhcrc.org/science/phs/progress_study/index.html

If you would like a copy of any of our recent or upcoming papers, or if you have any questions, or would like to report any family updates or changes in your current address or phone information, please feel free to contact us.