A letter from Dr. Ian Krantz a geneticist at CHoP regarding the ongoing and future research of Pallister-Killian Syndrome.

September 5, 2008

In terms of the research we (CHoP and involved doctors) are interested in 2 main areas:

1) Clinical: We would really like to collect as much detailed clinical information on as many individuals with PKS as possible so that we can more comprehensively understand all of the clinical issues and natural history of PKS so as to establish better treatment and management guidelines for individuals at all ages. Towards this end we would ask families to sign a research consent and to either send their medical records and or clinical summaries on their children or sign releases so we can request the information directly from their health care providers. The goal is to take all of this information and create a comprehensive on-line clinical database that eventually would be available to the medical community for queries (obviously with all identifiers removed).

2) Molecular: We are in the process of collecting both blood and skin samples (preferably obtained simultaneously - but can be done at different times or just one or the other-- we can also have labs send us cell lines established from skin biopsies that may have been done in the past) from as many individuals with PKS as possible to do some basic science research looking at a number of issues:

a) We want to see if by using the new array technologies for chromosomal analysis if we can detect the chromosome 12p differences in the blood samples in children where using standard diagnostic techniques it was not detected. This would have diagnostic implications since if it is able to be detected then I would suspect that once the new technology becomes more widespread as a clinical diagnostic tool, then more children will be diagnosed with PKS than currently as many clinicians do not think to do a skin biopsy to look at chromosomes if the blood is normal. I also think this will expand the clinical spectrum of what we know as "PKS" as milder individuals will be diagnosed who clinicians may not recognize clinically as PKS and have had normal blood chromosome testing.

b) Using the fibroblasts we want to look at all of the genes in the cell ("the genome" and see which genes are turned on or off at different levels in kids with PKS as compared to unaffected controls. These "expression" studies will allow us for the first time to understand which genes are actually contributing to the clinical features we see in PKS. Although we know that having extra copies of the short arm of chromosome 12 results in PKS there are some kids with 22 extra copies, some with one extra copy, and

some with only small parts of the short arm extra...we believe that some genes on the short arm are likely acting as "master switches" and effect many other genes that may be on many different chromosomes. By doing expression studies to look at all of the genes in a cell we can see what is actually be affected. In order to do this we would need at least 25 skin samples in order to be sure that what we are seeing is consistent across all kids with PKS...we currently have about 15 samples so we are getting close.

c) We are also interested in defining a "minimal critical region" on chromosome 12p, i.e. what is the smallest region on 12p that when duplicated results in PKS...by doing this we hope to define which genes are the critical genes on 12p that cause the clinical features of PKS.

These are the first steps towards really understanding what is happening at a very basic cellular level that is causing the clinical manifestations seen in PKS. Once we find out exactly which genes are involved and understand what their role is, we ultimately hope that this will lead to the development of better management and ultimately treatments for kids with PKS. Of course none of this happens in a vacuum and relies on the support of families and your Foundation, and we will need to raise funds for this research (these experiments are very expensive!!). Once we have some preliminary data we will start writing grants to the NIH (National Institutes of Health) and March of Dimes to get this funding!

Ian Krantz, M.D.

Associate Professor of Pediatrics
Director, Medical Genetics Training Program
The Children's Hospital of Philadelphia
1007-C ARC
3615 Civic Center Blvd
Philadelphia, PA 19104
Tel. (215) 590-2931
Fax. (215) 590-3850
ian2@mail.med.upenn.edu