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Singapore scientists describe novel method for 3-D whole genome mapping research

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In this week's *Nature,* Genome Institute of Singapore (GIS) scientists report a technological advance in the study of gene expression and regulation in the genome's three-dimensional folding and looping state through the development of a novel technology.

The technology is ChIA-PET (Chromatin Interaction Analysis using Paired End Tag sequencing). Chromatin is a complex combination of DNA and proteins that make up chromosomes.

"Many studies have found that regions of the genome which are not near genes are very important in controlling disease," said Melissa Fullwood, Ph.D., first author of the research paper and member of a team of GIS scientists led by Yijun Ruan, Ph.D., Senior Group Leader and Associate Director of Genomic Technologies, and Senior Research Scientist Edwin Cheung, Ph.D.

"In thinking about how this can happen, many scientists hypothesized that chromatin interactions - 3-dimensional loops in DNA - might be what allow these regions to remotely talk to genes," Dr. Fullwood added.

"The subsequent discovery of chromatin interactions between specific genes and specific enhancer sites generated a lot of interest to find chromatin interactions throughout the entire genome. Our study is one of the first to be able to address this 'Holy Grail' of genomics,'" she said.

Ever since the human genome was found to be organized in a three-

dimensional (3D) manner rather than in a two-dimensional linear fashion, scientists have been challenged to find an effective method to study the regulation of gene activity that took into account the complexities of its 3D structure.

Using ChIA-PET technology, the GIS scientists have successfully met the challenge and confirmed the presence of genome-wide long-range chromatin interactions.

Using the oestrogen receptor-α (ERα) as a model, the GIS scientists investigated how the human genome was organized in response to oestrogen signalling to control the expression of genes in breast cancer cells. They discovered that extensive ERα-bound long-range chromatin interactions in the human genome were involved as a primary mechanism for regulating estrogen-mediated gene expression.

"Our institute had been working to develop this technology to answer a fundamental question in cancer. These results show us that higher order DNA interactions on a genome scale can explain some of the contradictions in older studies. This work will pave the way for the development of highly specific anti-hormone treatments in breast cancer," said Edison Liu, M.D., Executive Director of GIS, one of the research institutes sponsored by Singapore's Agency for Science, Technology and Research (A*STAR).

"The study represents a true scientific tour de force. It shows a massive genome wide scale the interactions between a specific set of enhancers and the genes they regulate. The approach and results shown here will certainly be well received by the large community studying gene regulation," said Edward Rubin, M.D., Ph.D., Director of the Genomics Division at the Lawrence Berkeley National Laboratory, University of California, Berkeley, and Director of the U.S. Department of Energy Joint Genome Institute. Dr. Rubin is a member of the GIS Scientific

Advisory Board.

The ChIA-PET methodology and the ERα-bound human chromatin interaction map represent the starting point of an entirely new field for scientists to study how the human genome is folded in order to communicate the codes in regulating gene expression. Crucial for unravelling the mechanisms of genome control during cell differentiation, ChIA-PET and the chromatin interaction map may lead to a better understanding and control of diseases. This method was based on a revolutionary gene sequencing method known as paired-end ditag (PET) sequencing, which was pioneered in 2005 by GIS scientists, led by Senior Group Leaders Yijun Ruan, Ph.D., and Chia-Lin Wei, Ph.D.

More information: The research findings are reported in the Nov. 5, 2009 issue of *NATURE* in a paper titled, "An Oestrogen Receptor α-bound Human Chromatin Interactome".

Source: Agency for Science, Technology and Research (A*STAR), Singapore