Scientists find link between estrogen metabolism pathway and breast cancer risk

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Scientists at the Genome Institute of Singapore (GIS), a biomedical research institute of the Agency for Science, Technology and Research (A*STAR), and the Karolinska Institutet, Sweden, recently discovered that DNA polymorphisms related to the production of estrogen play an important role in the development of hormone-sensitive breast and endometrial cancer. The knowledge gained may help develop better measures for the prevention and treatment of breast cancer.

This study is the most comprehensive genetic research of the estrogen metabolism pathway involving 7577 participants from Sweden and Finland. It is able to overcome many limitations of previous studies which usually investigated a limited number of single nucleotide polymorphisms (SNPs) within some candidate genes through single SNP analysis, often in a moderate number of study subjects, leading to inconsistent results across different studies.

Led by GIS Executive Director Prof Edison Liu, GIS Senior Group Leader Dr Liu Jianjun and Prof Per Hall, Medical Director of the Karolinska Institutet, the finding was published in PLoS Genetics on July 1, 2010.

"Previous studies have typically looked at single genes and have produced inconsistent results. Genes work together in complex networks. By using a systematic approach to interrogate the network of genes that affects hormonal exposure and hence risk of breast and endometrial cancers, we found a small group of genes which works together to affect

cancer risk," said first author, Dr Low Yen Ling. "The results of this study has moved us one step closer to understanding the common pathways which are involved in the development of breast cancer and endometrial cancer." Dr Low, who was involved in this research while she was at the GIS, is currently a Clinical Scientist at the Abbott Asia-Pacific Nutrition Research & Development Center.

Similarly, Prof Edison Liu said, "This research raises the possibility of having a test using multiple genetic markers that, when added together, can give an estimate of risk for the most common forms of breast cancer. Previously such genetic risk determination was limited to rare forms of breast cancer. It was the combination of the markers rather than single markers, and our integration of the knowledge of the estrogen metabolism pathways that made the difference."

Director of the NUS-GIS Centre for Molecular Epidemiology, Prof Chia Kee Seng added, "This study is the result of a very strong collaboration between the Genome Institute of Singapore and the Karolinska Institutet. Swedish and Finnish samples were analysed at GIS and the subsequent joint analyses resulted in a deeper understanding of the complex genetic mechanisms of hormone metabolism and how this leads to breast and endometrial cancer."

In this study, several hundreds of SNPs were analyzed in a large clinical sample consisting of 7577 participants from Sweden and Finland. The SNPs were analyzed in groups that were categorized according to their potential biochemical functions in the production of estrogen, and the accumulative effect of multiple SNPs within a group on breast cancer development was tested. The scientists found a positive association of breast cancer risk with the DNA variation of the genes involved in the production of estrogen, including the CYP19A1 gene that produce aromatase enzyme.

"Aromatase (coded by CYP19A1) is used to produce estrogen from androgen in postmenopausal women. As estrogen exposure is the most important risk factor for breast cancer, inhibiting aromatase activity and thus lowering estrogen production has been commonly used to treat breast cancer in postmenopausal women," said Dr Liu Jianjun. "The current study advanced our understanding of aromatase by demonstrating that the modulation of aromatase activity by either DNA variation or pharmacological agents can both influence the development of estrogen-sensitive tumour in postmenopausal women. The convergence of genetic and pharmacological effects of CYP19A1 also suggested that other genes involved in the production of estrogen from androgen can act as potential therapeutic targets for treating breast cancer. In addition, the finding of this study raises the possibility that breast cancer can be prevented by blocking the production of estrogen through the use of an aromatase inhibitor."

Prof Per Hall added, "The findings published in *PLoS Genetics* are truly exciting and reassuring. Given the central role of estrogen in the carcinogenesis of breast cancer, researchers have for decades tried to link genetic variation in the estrogen metabolizing pathway to the risk of breast cancer. For the first time, we find compelling evidence that there is a strong link between polymorphisms in genes that metabolize estrogen and risk of both breast and endometrial cancer. The fact that polymorphism in the aromatase gene, CYP191A1, influence the susceptibility to breast cancer, strengthen the utility of the well-established aromatase inhibitors as chemoprophylaxis agents for targeted subgroups of women identified to have an increased risk of breast cancer."

Provided by Agency for Science, Technology and Research (A*STAR)

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