香港大學李嘉誠醫學院
香港沙宣道二十一號

The University of Hong Kong
Li Ka Shing Faculty of Medicine
21 Sassoon Road, Hong Kong

Press Release

HKU Discovers New Mechanism in the Causation of Hereditary Colon Cancer – "Good Gene in a Bad Neighbourhood"

Colon Cancer

Colon cancer is the second most common cancer in Hong Kong, and its incidence has risen rapidly in the past 20 years. Most colon cancer occurs in the age of 50 or above, and is mainly related to diet and environmental factors.

However, around 10% to 15% of all colon cancer cases have a hereditary basis. The most common type is **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**, which accounts for 4% of all colon cancer. The Hereditary Gastrointestinal Cancer Genetic Diagnosis Laboratory, Department of Pathology, The University of Hong Kong and Queen Mary Hospital has shown that HNPCC accounts for a large proportion of local patients with familial or early-onset colon cancer. The research team has previously discovered a new mechanism causing HNPCC by heritable methylation. Recently the research team has uncovered the mechanism causing heritable methylation in these families, which is caused by a good anti-cancer gene being locked up by a bad neighbour. This ground-breaking research was published in the leading scientific journal *Nature Genetics* in January, 2009.

Research Background

HNPCC patients have no symptoms until cancer develops. The most important clues to suspected cases of HNPCC are occurrence of colon cancer in multiple family members, multiple cancers in a single individual, and the onset of the cancer at an early age. HNPCC is known to be caused by inheritance of a mutation that inactivates one of the DNA **mismatch repair (MMR)** genes, which can be detected by a blood test for genetic diagnosis. A normal human gene generally has three components, a promoter switch to control the "on" or "off" of the gene, a protein coding part, and a termination signal to denote the end of the gene. Most MMR gene mutations change the protein encoding part of the gene, leading to errors in protein production, which in turn predisposes the individual to develop cancer. The mutated DNA code is found in every cell of the body, with a 50% chance of inheriting to the off-spring. Genetic diagnosis by DNA sequencing to look for the mutated DNA code in blood cells can help assess cancer risk accurately in the affected family, and facilitate planning of cancer prevention strategies. However, in some HNPCC families, the DNA codes of their MMR genes are completely normal. Thus standard genetic testing may not detect the underlying gene defect, resulting in substantial psychological burden for the whole family.

Research Methods and Findings

Supported by the Hong Kong Cancer Fund, the Michael and Betty Kadoorie Cancer Genetics Research Programme and the Research Grants Council of the Hong Kong Special Administrative

Region, the research team of the Hereditary Gastrointestinal Cancer Genetic Diagnosis Laboratory has been providing a hereditary colorectal cancer genetic diagnosis service for Hong Kong people, and also studying new mechanisms for the causation of HNPCC. Through DNA sequencing for MMR genes in blood cells, the team has successfully identified the mutation in over 100 local HNPCC families. However, in a small number of families, the DNA codes of their MMR genes are completely normal. Through studies into these families, the research team discovers a new mechanism for HNPCC – promoter methylation.

Promoter of a gene is like a switch that controls the "on" and "off" of a gene, and methylation "locks" it into a permanent "off" position. If methylation turns off an anti-cancer gene, such as a MMR gene, the result is a loss of function of the gene which eventually leads to the development of cancer. Previously, the cause of abnormal methylation in cancer remained unknown.

In the past, it is believed that mutation usually lies within the disease-causing gene itself. Thus genetic testing only studies the disease-causing gene and does not cover the neighbouring genes. However, in two local Chinese HNPCC families, as well as 4 Dutch HNPCC families residing in the Netherlands, the Hong Kong and Dutch research teams (lead by Professor S.Y. Leung and Dr. T.L. Chan from the Department of Pathology, The University of Hong Kong, and Dr. Marjolijn Ligtenberg in Radboud University Nijmegen Medical Centre of The Netherlands) have concurrently found a deletion mutation in a gene, named TACSTD1, residing immediately adjacent to the MMR gene MSH2. The deletion removed the transcriptional termination signal of TACSTD1 (signal that determines boundaries between genes). As a result, the mutated neighbouring gene interferes with the activity of the MSH2 gene, causing the MSH2 gene promoter to be methylated, thus switched it "off" and locks it into a permanent "off" position. This mutation causes cancer development in the colon or endometrium in multiple members of these families, in individuals as young as 18 to 20 years of age. This is the world's first report of deletion of transcriptional termination signal in a neighbouring gene, causing heritable methylation and hereditary cancer syndrome in humans.

Impact of the Study

1. The study shows that disease-causing mutation can reside in a neighbouring gene instead of the disease-causing gene itself. Thus a good gene in a bad neighbourhood can also cause hereditary diseases. This finding has revolutionized the way genetic diagnosis on hereditary disease is performed. Genetic tests should not be limited to examining the disease-causing gene, but also extended to study the termination signals of the neighbouring genes. The study will help many families with different types of hereditary diseases to uncover the disease-causing mutation and improved the success rate of prevention and treatment.
2. The study also illustrates a new mechanism causing gene methylation, by deletion of termination signal in a neighbouring gene. Since abnormal methylation is closely linked to cancer development, our findings will be useful for developing new anti-cancer drugs aiming at changing the methylation patterns of cells.

Importance of HNPCC Research and Genetic Diagnosis Service

Hong Kong's young population has a uniquely high incidence of colon cancer. A significant proportion of these cases are due to HNPCC. Genetic diagnosis can accurately identify individuals who carry mutation in the MMR genes, and distinguish amongst family members who have or have not inherited the mutated gene. For family members who have not inherited the mutation, they can be relieved of the psychological burden. And for those who have inherited the mutation, regular preventive screening can be conducted, which is highly effective

in reducing cancer incidence and mortality.

The Hereditary Gastrointestinal Cancer Genetic Diagnosis Laboratory, Department of Pathology, The University of Hong Kong and Queen Mary Hospital, studies the genetic basis of hereditary colon cancer, and provides genetic diagnosis service for patients at risk. The Laboratory has set up a charitable patient referral centre – Hereditary Gastrointestinal Cancer Registry – in St. Paul's Hospital. The Laboratory and the Registry collaborate with major local public and private hospitals to provide free genetic diagnosis, counselling and psychosocial support services for patients in need. This programme is supported by the Hong Kong Cancer Fund, aiming to achieve cancer prevention in high-risk populations. For further details, please visit the website of the Laboratory at http://www.hku.hk/patho/colonreg or by phone at 28303729.

Please visit the website at http://web3.hku.hk/facmed/hkumed/news_list.php for press photos and supplementary information.

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新聞稿

港大發現遺傳性大腸癌新發病機制 - 良好基因之壞鄰居

大腸癌

在過去二十年，香港的大腸癌個案不斷上升，現已成為香港最常見癌症的第二位。大腸癌多發生於五十歲以上，成因相信與食物、環境等因素有關。

據統計，10%至15%的大腸癌屬遺傳性，其中以「**遺傳性非瘜肉結直腸癌綜合症**」最為常見，佔大腸癌患者4%。據香港大學及瑪麗醫院病理學系「遺傳性腸胃癌基因診斷化驗室」研究顯示，本港年輕或家族性大腸癌患者中，不少患「遺傳性非瘜肉結直腸癌綜合症」。該化驗室早前已發現一種由遺傳性甲基化導致「遺傳性非瘜肉結直腸癌綜合症」的新機制，最近該研究小組在這些家庭中發現導致遺傳性甲基化的原因——毗鄰的突變基因扣鎖良好的抑制癌症基因。此項突破性研究成果，已於二零零九年一月在國際權威科學雜誌《自然遺傳學》上發表。

研究背景

「遺傳性非瘜肉結直腸癌綜合症」患者，於癌症發生前並無明顯病徵；一般只能透過家族病歷推測，其特徵為：多名家族成員患癌、病人同時患上超過一個或一種癌症、以及年輕發病等。以往所知，「遺傳性非瘜肉結直腸癌綜合症」的致病機理為患者遺傳了突變的「**錯配修補基因**」。**錯配修補基因**為抑制癌症的基因。一個正常的基因由三個部分組成，包括啟動子控制基因的「開」及「關」、製造蛋白部分及終止訊號。最常見引起「遺傳性非瘜肉結直腸癌綜合症」是**錯配修補基因**突變破壞基因的編碼，導致製造蛋白質過程出錯，大大增加患癌機會。突變的 DNA 編碼存在於身體所有細胞，並有一半機會遺傳給子女。患者及其親屬可透過抽血作基因診斷，進行 DNA 排序，找出編碼錯誤部分，更準確評估患癌機會，及早作出適當的預防措施。

但小部分患有「遺傳性非瘜肉結直腸癌綜合症」的家庭，其**錯配修補基因**完全正常，以致一般的基因診斷未能找出問題癥結，對患者家庭構成沉重心理包袱。

研究方法及結果

「遺傳性腸胃癌基因診斷化驗室」一向致力為港人進行遺傳性腸胃癌基因診斷及研究「遺傳性非瘜肉結直腸癌綜合症」嶄新致病機理，經費由香港癌症基金會、嘉道理癌病基因研究計劃及香港特別行政區政府的研究資助局支持。「化驗室」過去以患者血液進行**錯配修補基因**的DNA排序，已成功為超過一百個患有「遺傳性非瘜肉

結直腸癌綜合症」的家庭找出突變基因。然而，小部分患有「遺傳性非瘜肉結直腸癌綜合症」的家庭之**錯配修補基因**正常，透過研究這些家庭，研究小組發現成因涉及一種嶄新的機制——**基因啟動子的「甲基化」**。

基因受啟動子控制，一旦啟動子甲基化，基因就被「上鎖」關閉，若甲基化「關閉」的是抑制癌症的基因，如錯配修補基因，便會影響細胞正常運作，引致癌症。過往醫學界仍然不明白導致啟動子異常甲基化的成因。

以往科學界相信，基因突變通常發生在致病基因本身，因此基因檢測只注意疾病基因而忽略鄰近的基因。研究小組分別由香港大學病理學系梁雪兒教授及陳俊良博士，和荷蘭奈梅亨瑞德榜德大學醫學中心Dr. Marjolijn Ligtenberg 帶領下合作進行，從兩個本地的華人「遺傳性非瘜肉結直腸癌綜合症」家庭及四個居住荷蘭的荷蘭裔家庭中，在錯配修補基因MSH2的毗鄰基因TACSTD1發現「缺失」突變，擾亂TACSTD1基因轉錄的終止訊號；這突變掃除了兩基因間的藩籬，引致TACSTD1基因干預錯配修補基因MSH2之運作，令MSH2基因啟動子甲基化，錯配修補基因此被「上鎖」關閉。這是引起上述家庭成員患早發性結腸或子宮內膜癌的原因，其中最年輕患者只有十八至二十歲。這是全球首份因鄰近基因缺失終止訊號引致人類遺傳性甲基化和遺傳性癌症綜合徵狀之研究報告。

研究結果的重要性

1. 癌症的成因並不一定由致癌基因本身問題導致，亦可由鄰近的基因突變引起；「城門失火殃及池魚」。此研究發現徹底改變遺傳性疾病的基因診斷方法。基因測試不應局限於檢查致癌基因本身，應擴大基因測試範圍至鄰近基因的終止訊號，幫助更多有遺傳性疾病的家庭找出致病原因，提升預防及治療成功率。
2. 因缺失終止訊號，令鄰近的基因甲基化導致癌症，為嶄新的致癌機制，加深科學界對「甲基化」的了解。由於基因異常「甲基化」與癌症關係密切，新發現有助開發新藥物，藉改變癌細胞的「甲基化」模式，達致抗癌目標。

「遺傳性非瘜肉結直腸癌綜合症」研究及基因診斷的重要性

香港的大腸癌患者中，年輕患者的比例特別高，當中不少是「遺傳性非瘜肉結直腸癌綜合症」患者。基因測試可準確為病人及家屬檢驗引致「遺傳性非瘜肉結直腸癌綜合症」的突變基因，從而分辨是否遺傳了致病基因。如果確定為非患者，便可放下不少心理包袱。至於帶有「遺傳性非瘜肉結直腸癌綜合症」基因人士，只要及早接受定期預防性檢查，可大大減低癌病的發病率和死亡率。

「遺傳性腸胃癌基因診斷化驗室」隸屬香港大學及瑪麗醫院病理學系，致力研究遺傳性大腸癌的成因，及為患者提供基因診斷服務。化驗室在聖保祿醫院亦成立了一間慈善性的病人轉介中心 — 「遺傳性腸胃癌支援中心」。化驗所和支援中心與各大公立和私營醫院合作，免費為有需要的病患者及其家屬作基因診斷、輔導和情緒支援服務，經費由香港癌症基金會支持，以達致為高危人士預防癌症的目標。化驗室網址為： http://www.hku.hk/patho/colonreg (電話：28303729)

如欲索取補充資料，請瀏覽網址：http://web3.hku.hk/facmed/hkumed/news_list.php

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