Molecular Genetics of Early-onset Colorectal Cancer

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Dr Chan graduated from the University of Newcastle Upon Tyne (UK) and gained his PhD degree at The University of Hong Kong in 1999. He has been promoted to Research Assistant Professor in the Department of Pathology at HKU since 2004.

His main research interest is in the molecular genetics of colorectal cancer (CRC). In collaboration with his mentors, Dr SY Leung and Dr ST Yuen, they have performed a series of research studies to illustrate the factors contributing to the high frequency of early-onset colorectal cancer in local population and set up the protocols for genetic diagnosis of familial CRC. Nowadays, hundreds of families are beneficiary under these studies. In addition, they have been trying to dissect the molecular pathways of CRC. This approach improves our understanding of tumourigenesis of CRC and leads the research group to verify the possibility of alternative pathway, such as the serrated pathway, of CRC other than the well-known adenoma-carcinomas pathway. Recently, they have been involved in the development of novel method for the detection of familial CRC without detectable mutation.

Colorectal cancer (CRC) is the second most common cancer and affecting more than 3,500 patients in Hong Kong in 2002. We have previously observed a special epidemiology pattern in the patients with early-onset (<46 years of age at diagnosis) colorectal cancer in local population. Hereditary non-polyposis colorectal cancer (HNPCC), hitherto, is the most frequent familial cancer syndrome which contributes 2 to 3% of total number of colorectal cancer. We have demonstrated that germline mutation of mismatch repair genes, which are the causative genes of HNPCC, represents a significant portion of early-onset CRC (Chan *et al.* J Natl Cancer Inst. 1999;91:1221). Detailed analysis further revealed that recurrent mutation can be responsible for one third of the affected families in our Hereditary Gastrointestinal Cancer Registry (Chan *et al.* Oncogene. 2001;20:2976, Chan *et al.* Am J Hum Genet. 2004;74:1035). For *MSH2* c.1452-1455delAATG, which is the most frequently recurrent mutations, we designed a specific PCR-based diagnostic test on paraffin-embedded tissues and identified the same mutation in 2 of 138 consective patients with early-onset CRC. Haplotype analysis was performed using microsatellite markers flanking the *MSH2* gene. A common disease haplotype can be identified in all families sharing the same mutation, which suggests a founder effect. Further analysis indicated that these families originated from the Chinese province of Guangdong and the age of the specific disease haplotype may date back to between 22 and 103 generations ago. Our data has important implications for the design of mutation-detection strategies for the southern Chinses population. Since there were major emigrations from Hong Kong and Guangdong province during the 19th and 20th centuries, this finding is also significant for Chinese communities worldwide.