

# Hereditary Colorectal Cancer Syndromes in Hong Kong: a Registry's Perspective

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**Key words:** registry, hereditary colorectal cancer, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer

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Submitted: 6 October 2005

Accepted: 14 October 2005

## Abstract

Established in 1995, the Hereditary Gastrointestinal Cancer Registry aimed at cancer prevention due to hereditary colorectal cancer syndromes in Hong Kong through early detection, timely treatment, education and ongoing research. This article details the history, structure and work of the Registry. A summary is also provided on the results of various research work conducted by the Registry which facilitates the clinical management of hereditary colorectal cancer syndromes in Hong Kong Chinese families.

## Introduction

Hereditary colorectal cancer (HCRC) accounts for 5-10% of all colorectal cancers [1]. In Hong Kong, colorectal cancer (CRC) is the second most common malignancy [2]. In a study, our group drew attention to the distinct epidemiology in the Hong Kong Chinese population, in which there is an incidence of CRC in the young population (<50 years of age at diagnosis) that is four times the rate in other countries, such as the United States, Scotland and Japan [3]. Subsequent studies showed that a significant proportion of these patients actually suffered from HCRC.

## Hereditary Gastrointestinal Cancer Registry

### History

To fill the gaps in our knowledge and service needs, the Hereditary Gastrointestinal Cancer Registry was

established in Hong Kong in 1995 through the effort of a colorectal surgeon and a gastrointestinal pathologist. The Registry is based at Queen Mary Hospital, which is one of the teaching hospitals in Hong Kong where these two doctors work. To the best of our knowledge, it is the first registry of such kind in China.

When newly established, the Registry was mainly supported by research grants, individual donations and the generosity of the two involved departments at Queen Mary Hospital. In the past five years, however, the Registry has been largely supported by the Hong Kong Cancer Fund, which is a local charitable organisation.

### Members

The Registry is composed of three divisions: clinical, laboratory and psychosocial teams.

The clinical team consists of a colorectal surgeon, a Registry coordinator and a clerical assistant. Apart from

**Table 1.** Entry criteria of the Hereditary Gastrointestinal Cancer Registry

1. Families affected by histologically proven Familial Adenomatous Polyposis (FAP) or other polyposis syndrome. This includes index patients and at-risk first-degree relatives above the age of 12 years.
2. Families affected by Hereditary Non-Polyposis Colorectal Cancer (HNPCC) satisfying the Amsterdam Criteria, the modified Amsterdam Criteria and/or with proven germline mismatch repair gene mutation. This includes index patients and at-risk first-degree relatives above the age of 25 years.
3. Suspected HNPCC families satisfying one of the following criteria: <ul style="list-style-type: none"> <li>• An individual has histologically proven colorectal cancer diagnosed before the age of 45 years;</li> <li>• An individual has two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or associated extra-colonic cancers;</li> <li>• An individual has histologically proven colorectal cancer and a first-degree relative has histologically proven colorectal cancer or HNPCC-related extra-colonic cancers. At least one of these cancers is diagnosed before the age of 45 years;</li> </ul> <p>For these families, we recruit both index patients and at-risk first-degree relatives above an age five years younger than the youngest age of cancer diagnosis in the family; Extra-colonic cancers include: cancers of the stomach, small bowel, uterus, ovary, brain and transitional cell carcinoma of the urological tract.</p>

looking after clinical and screening activities, the clinical team is also responsible for overall administration and day-to-day running of the Registry. Surgeon liaisons in other hospitals assist in family recruitment as well as clinical screening and management.

The laboratory team consisting of a pathologist, a scientist and a laboratory technician is responsible for tissue molecular analysis and genetic testing. Pathologist liaisons in other hospitals participate in systemic case finding for hereditary non-polyposis colorectal cancer (HNPCC) and provide assistance in tumour tissue tracing.

The newly established psychosocial team consists of a clinician (a colorectal surgeon), a part-time clinical psychologist and a part-time research assistant. In collaboration with two academic staff (one from the Department of Social Work and another from the Department of Psychology) of the University of Hong Kong, the psychosocial team provides psychosocial support to recruited families.

Apart from the provision of service, the three teams are also active in conducting research in their respective fields to improve our understanding of Chinese families with HCRC.

**Mission & Recruitment**

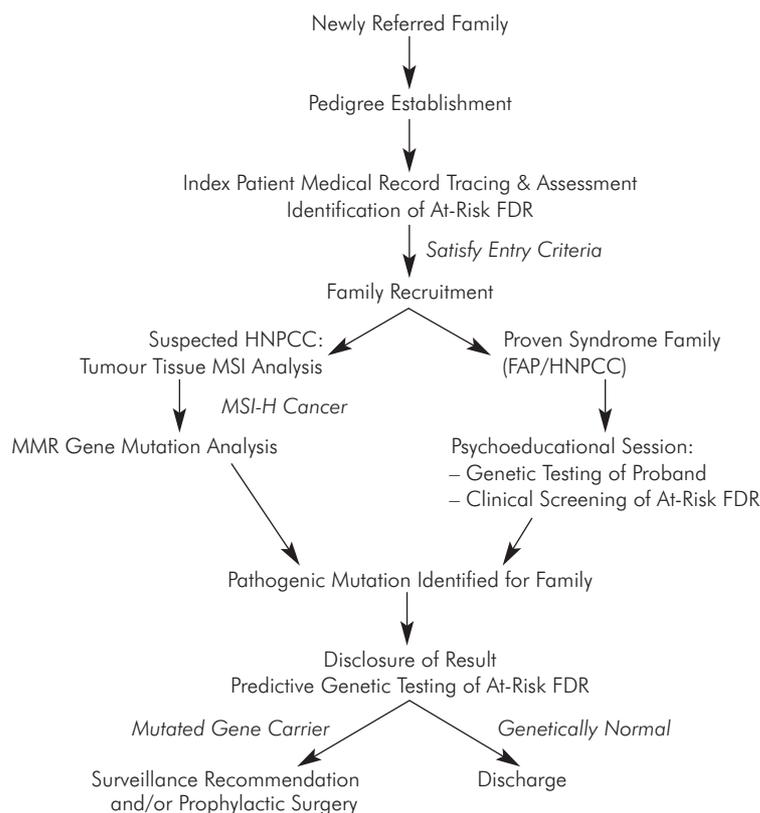
The mission of the Registry is to prevent colorectal cancer in high-risk families through early detection, timely treatment, education and ongoing research. Our service targets are families in Hong Kong suffering or suspected to be suffering from HCRC syndromes.

The entry criteria of the Registry are shown in Table 1. We accept voluntary referrals from both the medical profession as well as affected families themselves over the whole territory of Hong Kong. Besides, the Registry has a research protocol for systemic case finding of HNPCC conducted in three public hospitals in Hong Kong. Together, these three hospitals treat about 25% of all CRC diagnosed in the whole city. For these hospitals, all resected CRC specimens of patients diagnosed before 50 years old would be subjected to microsatellite instability (MSI) analysis. Those patients with high level of microsatellite unstable (MSI-H) CRC would be contacted to obtain consent for further analysis of germline mismatch repair (MMR) gene mutation.

Up to June 2005, the Registry has recruited 582 families satisfying our recruitment criteria. Four hundred and forty-three families (76.1%) were referred from 18 public hospitals, among which 327 families (56.2%) were identified through the systemic case finding research protocol. Of the remaining, 111 families (19.1%) were self-referrals and 28 families (4.8%) were referred by surgeons working in the private sector.

Based on a combination of clinical and molecular criteria, we have identified 159 families suffering from HCRC syndromes. This includes 99 HNPCC families, 51 familial adenomatous polyposis (FAP) families, five Peutz Jegher's syndrome families and four juvenile polyposis families.

Molecular genetic analysis so far has identified 32 families with germline APC gene mutation, 63 families with germline MMR gene mutation (18 *hMLH1*, 42 *hMSH2* and 3 *hMSH6*) and four families with germline



N.S.:FDR – first-degree relative  
 HNPCC – hereditary non-polyposis colorectal cancer  
 FAP – familial adenomatous polyposis  
 MSI – microsatellite instability  
 MSI-H – high level of microsatellite instability  
 MMR – mismatch repair

**Fig. 1.** Workflow of the Registry for newly referred families

*STK11/LKB1* mutation. Two hundred and twenty-eight individuals were proven to be mutation carriers in one of the above-mentioned genes. One hundred and forty-seven individuals from affected families were shown to be genetically normal and have been discharged from our care.

## Referral Work-Up & Management

Figure 1 details the workflow involved for newly referred families. Trained in pedigree establishment, our Registry coordinator would contact the family directly to obtain a detailed family history. A pedigree including information on at least three generations with maximal lateral extension would then be established. For cancer patients in the family, information regarding the type of cancers, the age at cancer diagnosis and their

relationship with each other would be obtained. At-risk first-degree relatives (FDR) would also be identified.

For those families with histories apparently satisfying the Registry's entry criteria, consent would be obtained for recruitment and for tracing the medical record of index patients for further assessment. In Hong Kong, legislation requires that a patient's medical record and tissue sample be kept for seven years only. Therefore, records and tissue of those cancer patients treated more than seven years prior to recruitment may not be accessible. Hence, cancer diagnosis for some families may have to be assumed without histological confirmation and tissue molecular analysis for these families may not be possible.

Counselling will be offered before and after genetic testing. During counselling, emphasis will be put on

the pros and cons of genetic testing. A cooling period will then be offered before a final decision is made by an individual regarding genetic testing. Our previous study on decisional consideration process regarding genetic testing [4] is helpful in devising counselling strategy. We found that our Chinese subjects were relational-orientated, that is, their decision would be affected more by the well-being of their significant others than themselves. Hence, emphasis would be placed on the implication of genetic testing for a subject's significant others.

Clinical surveillance of mutation carriers of various syndromes are carried out at the referral hospitals or Queen Mary Hospital depending on the preference of the subjects as well as their doctors in the referral hospitals. So far, about 75% of such surveillance activities have been carried out at Queen Mary Hospital where the Registry is based. For MMR gene mutation carriers, the option of prophylactic surgery instead of continuous clinical surveillance would be discussed. For those individuals detected to have cancers upon surveillance or those individuals requiring prophylactic surgery, the Registry will arrange such surgical treatment at the respective specialty units.

## Clinical Research on HNPCC

### Clinical Predictors for MSI & MMR Gene Mutation Analysis

Relying solely on traditional clinical criteria will underestimate the incidence of HNPCC in Hong Kong Chinese. This fact can be exemplified by the results of one of the Registry's earlier studies [5]: of the 27 patients with identifiable germline MMR gene mutation, only one patient's family history satisfied the Amsterdam criteria.

Because MSI is a hallmark of CRC associated with MMR defects and it occurs in the vast majority of CRC in HNPCC [6], we investigated the distinct clinical features associated with MSI in young (<50 years old) Chinese CRC patients [7]. We found that the incidence of MSI increased significantly with decreasing age at cancer diagnosis: 50% for those <30 years old; 41% for those 30-39 years old; and 15.1% for those 40-49 years old (Armitage trend test  $p=0.002$ ). Upon multivariate analysis, the independent predictors for MSI were: young age at CRC diagnosis, tumour located at or proximal to the splenic flexure (that is, proximal tumour location), increasing number of FDR with CRC and a personal history of metachronous cancer.

In a subsequent analysis published in abstract form on a larger sample of CRC patients ( $n=333$ ), we found that 84 (25.2%) of these patients had MSI tumours among which 39 were caused by germline MMR gene mutation. While the clinical predictors for MSI were the same as the previous analysis, we identified the following as independent clinical predictors of germline MMR gene mutation: CRC diagnosis before 45 years of age (OR 3.59; 95%CI 1.42-9.07); proximal tumour location (OR 5.05; 95%CI 2.29-11.16); family history of CRC (OR 3.51; 95%CI 1.50-8.20); and family history satisfying the Amsterdam criteria (OR 14.05; 95%CI 4.37-45.19).

In another study investigating germline MMR gene mutation in young CRC patients, we found that the success rate of mutation detection varied with the strength of CRC family history [8]. For young patients with MSI-H CRC but no family history, only 29.4% had identifiable germline mutation. For those with MSI-H CRC and a positive family history, the rate of germline mutation increased to 76.5%. Furthermore, for those with family histories satisfying the Amsterdam criteria as well as MSI-H CRC, all had detectable germline MMR gene mutation.

Knowledge derived from the above three studies facilitates the Registry in selecting suitable patients for HNPCC genetic testing. The information also provides an estimate as to the success rate of such mutation detection.

### Founder Mutations & Mutation Detection Strategy

Identification of founder mutations has important implications in the design of a mutation detection strategy for a particular ethnic population. To date, our Registry has identified two founder mutations in Hong Kong Chinese.

In 2001, we reported a novel germline 1.8 kb deletion involving exon 11 of *hMLH1* gene, which was often missed by the usual PCR-based mutation detection method [9]. We devised a diagnostic test based on the duplex-PCR method to facilitate detection of this mutation. So far, this mutation has accounted for 11.1% of all *hMLH1* mutations identified by the Registry.

Last year, we reported on a unique germline *MSH2* c. 1452-1455delAATG mutation [10]. To date, this mutation has been identified in 14 local Chinese families and it accounts for 33.3% of all *hMSH2* germline mutations as well as 22.2% of all germline MMR gene mutations detected by the Registry. Our laboratory has designed a specific PCR-based

diagnostic test on paraffin-embedded tissue to facilitate mutation detection.

### Phenotypic Features of HNPCC Patients & Genotype-Phenotype Correlation

A clinical audit was conducted early this year for 138 proven MMR gene mutation carriers (38 *hMLH1*, 89 *hMSH2* and 11 *hMSH6*) including 80 men and 58 women from 57 families. The median age at the time of assessment was 45 years (S.D. 11.3; range 26-80). All these individuals followed the Registry's recommended clinical surveillance protocol (see below for details).

To date, 87 (63%) have developed malignancy, 15 (10.9%) have developed colorectal adenoma only and 36 (26.1%) have had no phenotypic manifestation. Those who have had malignancy have been significantly older than those without malignancy (median age  $49.5 \pm 10.9$  years vs.  $41.0 \pm 8.1$  years;  $p=0.000$ ). Those who have ever had phenotypic manifestation (cancer or colorectal adenoma) were also significantly older than those without phenotypic manifestation (median age  $46.0 \pm 10.7$  years vs.  $39.0 \pm 8.1$  years,  $p=0.000$ ).

CRC developed in 77 individuals and the median age at first CRC diagnosis was 37.5 years (S.D. 9.6; range 22-65). Forty-one (53.2%) of these individuals had their first CRC located at the proximal colon. Ten individuals (13.0%) had synchronous CRC and another 10 had metachronous CRC. Extra-colonic cancers developed in 26 individuals (7 men and 19 women). Gynaecological cancer was the commonest extra-colonic malignancy and was found in 16 women (27.6%) with a median age at diagnosis of 43 years (S.D. 6.9; range 29-51). Three women had more than one gynaecological cancer. The types of gynaecological malignancy were: 10 uterine, 6 ovarian and 3 cervical cancers. For all those

with malignancy, 32 (36.8%) had either synchronous or metachronous cancers.

Men with HNPCC were more likely to develop malignancy (70.0% vs. 53.4%; OR 2.03, 95%CI 1.01-4.11), particularly CRC (70.0% vs. 36.2%; OR 4.11; 95%CI 2.01-8.43). However, HNPCC women were more likely to develop extra-colonic malignancy (32.7% vs. 8.8%; OR 5.08, 95%CI 1.97-13.13). There was no difference in the current age and age at cancer diagnosis between men and women.

On correlating phenotype with individual MMR genes, we found that both *hMLH1* and *hMSH2* mutation carriers were significantly more likely to develop malignancy than carriers of *hMSH6* mutation (*hMLH1* vs. *hMSH6*: 76.3% vs. 27.3%, OR 8.59, 95%CI 1.87-39.41; *hMSH2* vs. *hMSH6*: 61.8% vs. 27.3%, OR 4.31, 95%CI 1.07-17.39). However, there was no difference in the age at cancer diagnosis with respect to the three MMR genes. Furthermore, *hMLH1* mutation carriers were significantly more likely to develop CRC than *hMSH6* mutation carriers (68.4% vs. 37.5%, OR 5.78, 95%CI 1.30-25.71). No significant difference was found in CRC rate between *hMSH2* and *hMSH6* mutation carriers. There was no difference in the age at CRC diagnosis among individuals with the three MMR gene mutations. There was also no difference in the rate and the age at diagnosis of extra-colonic malignancy among individuals with mutation in the three MMR genes, although the number of affected individuals was small.

### Clinical Surveillance & Prophylactic Surgery of MMR Gene Mutation Carriers

The clinical surveillance protocol for our MMR gene mutation carriers is detailed in Table 2. To date, regular

**Table 2.** Clinical Surveillance Protocol for Carriers of Germline Mismatch Repair Gene Mutation

	Starting age (year)	Interval (year)	Method
colorectal	25	age 25-35:2 years age >35:1 year	colonoscopy
gynaecological	25	age 25-35:3 years age >35:2 years	vaginal examination, endometrial aspiration, trans-abdominal/trans-vaginal ultrasound, serum ovarian tumour marker
urological	25	age 25-35: 3 years age >35:2 years	urine cytology, ultrasound kidneys & bladder
gastric (if positive family history)	25	age 25-35: 3 years age >35:2 years	upper endoscopy

clinical surveillance of the 138 MMR gene mutation carriers has detected 12 malignancies in eight subjects. There were 5 colorectal, 2 urological, 3 uterine, 1 ovarian and 1 cervical cancers. The majority of these cancers were detected at an early stage. So far, none of the eight individuals have died of these surveillance-detected malignancies.

Surveillance colonoscopy detected colorectal adenoma in 46 mutation carriers, including 15 who had no previous history of malignancy. Twenty of these individuals had a history of recurrent colorectal adenoma.

Prophylactic surgery has been performed on 10 mutation carriers. This includes prophylactic colectomy or completion colectomy in 6 individuals, prophylactic hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) in 3 women and simultaneous prophylactic colectomy and TAHBSO in another woman.

## Clinical Research on FAP

### Phenotype & Clinical Management

In a paper published in 2002 on 36 FAP families, the Registry reported that the strategy of pre-symptomatic diagnosis by screening and appropriate surgery reduced the incidence of CRC in FAP patients [11]. In our most recent update on 51 FAP families, we confirmed the previous observation.

This update included 151 documented FAP subjects (86 men and 65 women) from 51 families including three families with the attenuated phenotype. Forty-five of these subjects died before Registry recruitment.

The diagnosis of polyposis was made by screening in 58 individuals (30 men and 28 women), whereas the remaining 93 were diagnosed due to bowel symptoms. The median age at FAP diagnosis was significantly younger for those due to screening than those due to symptoms ( $28.0 \pm 14.0$  years vs.  $36.0 \pm 13.2$  years,  $p=0.000$ ). Upon diagnosis, 66 (71%) of those with bowel symptoms had already developed CRC, whereas only 4 (6.9%) of those diagnosed by screening had synchronous CRC ( $p=0.000$ ). Two subjects diagnosed by screening more than 10 years ago refused prophylactic surgery. Both later presented with bowel symptoms due to CRC and succumbed to malignancy. Even with treatment, 56 individuals diagnosed by bowel symptoms ultimately died from CRC except one. This gives a CRC mortality rate at 59.1% for this group of patients. For those diagnosed by screening, three (5.2%)

have died from CRC to date, including the two who refused prophylactic colectomy. Therefore, the overall mortality rate was significantly lower for FAP subjects diagnosed by screening than those diagnosed by symptoms (5.2% vs. 60.2%,  $p=0.000$ ). Moreover, the median age at FAP diagnosis was significantly younger for those without synchronous CRC than those with synchronous CRC ( $29.0 \pm 12.6$  years vs.  $40.0 \pm 12.7$  years,  $p=0.000$ ).

For the type of prophylactic colectomy, restorative proctocolectomy (IPAA) is the most commonly performed procedure for the classical profuse type of polyposis, whereas total abdominal colectomy with ileorectal anastomosis (IRA) is the procedure of choice for attenuated polyposis.

Apart from CRC, our FAP subjects are prone to develop other serious extra-colonic lesions. This can be illustrated by the clinical data of 106 FAP subjects (57 men, 49 women) recruited by the Registry up to June 2005.

Papillary thyroid cancer is the only extra-colonic malignancy identified in our subjects to date. Six female FAP subjects have developed papillary thyroid cancers: two before and four after the diagnosis of FAP. All except one of the thyroid cancers developed before 30 years of age. All six women survived after treatment.

Desmoid tumours occurred in 17 individuals (7 men and 10 women) at a median age of 36.0 years (S.D. 9.2; range 21-49) with significant morbidity. Regarding the location of desmoids, three occurred extra-abdominally, three were on the abdominal wall, seven were entirely intra-abdominal and four had both abdominal wall and intra-abdominal components (combined).

Two of the intra-abdominal desmoids occurred without previous abdominal surgery; one of the desmoids precluded colectomy and another precluded restorative proctocolectomy. For the remaining abdominal desmoids (on the wall or intra-abdominal), they occurred at a median interval of 2.5 years (S.D. 4.7, range 1-18) after colectomy.

Regarding treatment of desmoid tumours, we offered surgical resection for extra-abdominal and abdominal wall desmoids. Two out of three extra-abdominal desmoids recurred after resection, whereas all abdominal wall desmoids did not recur. For intra-abdominal and combined types of desmoids, we usually adopted conservative treatment which included expectant treatment and various medical therapies

**Table 3.** Endoscopic surveillance protocol for patients with familial adenomatous polyposis after prophylactic colectomy

1. Flexible sigmoidoscopy every 6 months after total abdominal colectomy and ileorectal anastomosis.
2. Pouchoscopy every 2 years after restorative proctocolectomy.
3. Upper endoscopy and duodenoscopy every 2 years for all patients.

unless complication occurred. Excision of the abdominal wall component was performed in one patient with combined desmoids without recurrence. Debulking surgery of intra-abdominal desmoids had been performed in three patients resulting in enterocutaneous fistula in one and recurrence in another two.

Six patients developed various complications due to their intra-abdominal desmoids. These complications and their corresponding treatment include: obstructive uropathy in four requiring ureteric stenting; uretero-enteric fistula in three requiring ureteric stenting and long-term prophylactic antibiotics against urinary tract infection; enterocutaneous fistula in three treated conservatively; bowel ischaemia in one requiring massive small bowel resection resulting in short gut syndrome; intestinal obstruction in one treated by intestinal bypass; and inferior vena caval (IVC) obstruction in one requiring IVC stenting. One of these patients ultimately died of sepsis due to a combination of short gut syndrome and obstructive uropathy.

The protocol of endoscopic surveillance for FAP patients after prophylactic colectomy is detailed in Table 3. Surveillance endoscopy revealed adenomatous polyposis in the remaining gastrointestinal tract in a number of them. Pouch adenomatous polyposis occurred in five patients at a median interval of 9 years (S.D. 3.7; range 7-15) after IPAA. Two of these patients were treated with sulindac (Merck Sharp & Dohme, Herts, UK) which had resulted in histological resolution of pouch polyposis in one [12].

Gastric and duodenal adenomata were detected in three and eight patients, respectively. Microadenomatous changes in the duodenal papilla were detected in 23 subjects at a median age of 35.0 years (S.D. 7.7; S.D. 21-47). The natural history of duodenal microadenoma and its malignant potential is unknown. In one patient, serial upper endoscopies documented progression of duodenal microadenoma to adenoma over five years.

### Genotype-Phenotype Correlation

In a previous analysis published in abstract form, we investigated genotype-phenotype correlation in 54

individuals from 21 FAP families with known APC gene mutation. We found no difference in the colorectal phenotype between those individuals with mutation before and after codon 1000 of the APC gene. After colectomy, individuals with mutations beyond codon 1000 had significantly higher incidence of dysplastic changes in the remaining gastrointestinal tract (23.8% before codon 1000 vs. 76.9% after codon 1000;  $p=0.004$ ).

### Conclusion

Establishment of the Hereditary Gastrointestinal Cancer Registry in Hong Kong allows comprehensive management of hereditary colorectal cancer syndromes in a multidisciplinary approach. Apart from contributing to the understanding of hereditary colorectal cancer in the Chinese population, the ongoing research of our group has yielded useful information facilitating clinical management of Hong Kong families affected by these complex hereditary syndromes.

### Acknowledgement

The authors would like to thank The Hong Kong Cancer Fund for financial support, and Dr S. T. Yuen and Dr T. L. Chan for performing molecular genetic analysis on recruited families.

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