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<td>Cowden syndrome (CS) is an autosomal dominant disorder characterized by multiple hamartomas and a high risk of breast, thyroid and other cancers. The susceptibility gene is PTEN. The etiology of this disorder is to determine the genetic role of PTEN in non-CS CS-like families or individuals. The PI has accrued 15 site specific breast cancer families, without known BRCA1 and BRCA2 mutations. No intragenic PTEN mutations were found in these families. To date, 70 CS-like families and individuals have been accrued. One occult germline PTEN intragenic mutation was found among these families. The mutation positive family has breast, thyroid and endometrial cancers. Unfortunately, only 5 other families have endometrial carcinoma. In summary, at least 1.5% of non-CS CS-like families carry occult PTEN mutations. This has implications for the proband and family with respect to cancer risk and surveillance. Our preliminary data may suggest that endometrial cancer is a true component of CS and the data suggests that the International Cowden Consortium clinical diagnostic criteria are robust. Further accrual of these CS-like families, enriching for endometrial cancer, will be achieved and PTEN analysis, including the promoter, pursued.</td>
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**Introduction**

Cowden syndrome (CS) is an autosomal dominant disorder characterized by multiple hamartomas and a high risk of breast, thyroid and other cancers (reviewed by Eng 1). The risk of breast cancer in affected women can range from 25-50% 2,3. The PI mapped the CS gene to 10q22-23 4 and subsequently identified PTEN, encoding a dual specificity phosphatase, as the or at least a major CS susceptibility gene 5. That PTEN is a major CS gene was subsequently confirmed by other groups 6-8. In addition, the PI has shown that germline PTEN mutations cause a proportion of Bannayan-Riley-Ruvalcaba syndrome (BRR), an autosomal dominant disorder characterized by megeencephaly, mental retardation, lipomatosis, and speckled penis, previously thought not to be associated with cancer 9.

Because CS is difficult to diagnose and is under-recognized and therefore under-diagnosed, the PI chairing the International Cowden Consortium synthesized a set of diagnostic criteria for the operational diagnosis of CS (Table 1) 10, initially for research purposes and now, for clinical diagnostic purposes as well.

Table 1. International Cowden Consortium Diagnostic Criteria for CS

**Pathognomonic Criteria**

Mucocutaneous lesions:
- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

**Major Criteria**

Breast CA
Thyroid CA, esp. follicular thyroid carcinoma
Macrocephaly (Megalencephaly) (say, \( \geq 97\% \text{ile} \))
Lhermitte-Duclos disease (LDD)

**Minor Criteria**

Other thyroid lesions (e.g. adenoma or multinodular goiter)
Mental retardation (say, IQ \( \leq .75 \))
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
GU tumors (eg uterine fibroids) or malformation

**Operational Diagnosis in an Individual:**
1. Mucocutaneous lesions alone if:
   a) there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or
   b) cutaneous facial papules and oral mucosal papillomatosis, or
   c) oral mucosal papillomatosis and acral keratoses, or
d) palmo plantar keratoses, 6 or more
2. 2 Major criteria but one must include macrocephaly or LDD
3. 1 Major and 3 minor criteria
4. 4 minor criteria

Operational Diagnosis in a Family where One Individual is Diagnostic for Cowden
1. The pathognomonic criterion/ia
2. Any one major criterion with or without minor criteria
3. Two minor criteria

The question of “cryptic” CS or the frequency of mutation-proven CS in individuals or families presenting with components of CS, such as breast cancer and/or thyroid cancer and/or endometrial cancer is important for the patient and his/her family with regard to medical management. In this regard, this proposal asks two main questions:

Task 1: What proportion of familial breast cancer only families have CS?

Task 2: What proportion of CS-like families, which do not make the full diagnostic criteria of the International Cowden Consortium (Table 1) have germline PTEN mutations, with its full implications, targeting cases and families that have breast and/or thyroid/endometrial cancer.

Body

Task 1: Germline PTEN mutations in breast cancer only families
To date, a total of 15 site specific breast cancer families that are mutation negative for BRCA1 and BRCA2 have been accrued and documented. All 15 are germline PTEN mutation negative. Approximately half of the affected tested individuals are heterozyous at PTEN IVS8+32T/G, thus excluding whole gene deletion. At this point, there is extensive data to show that gross gene deletion only results in BRR and even then, it is rare. Again, all this analysis has been performed from small amounts of DNA left from old samples used for BRCA searches or from paraffin-embedded archived material, thus making Southern analysis impossible on these particular samples.

The plans for Years 2 and 3 is to continue accrual of site specific breast cancer families without BRCA1 and BRCA2 mutations for PCR-based germline PTEN analysis. These hopefully will be from peripheral blood leucocytes, thus making Southern analysis possible. The promoter lies within or is 250 kb long. Efforts by our lab and other labs are beginning to determine which portion or all of this segment is the minimal “true” promoter. If feasible after these analyses, then promoter mutation analysis will be performed in these families as well.

It would also appear from recent data (from our lab and others) that PTEN can be silenced or “inactivated” by causes other than structural gene alteration (ie mutation or deletion) (eg, Dahia et al 1999 12). In this regard, the PI plans to extend Task 1 to include examination of PTEN expression using immunohistochemistry to delineate
whether structural and/or other epigenetic phenomena pertain in PTEN inactivation in breast carcinogenesis.

Task 2: Mutation Analysis in Non-CS Breast-Thyroid and/or Endometrial Carcinoma Families/Individuals ("CS-Like Families")
To date, a total of 70 individuals or families with a CS-like syndrome have been accrued and cancers and tumors in affected individuals have been documented either with pathology report (preferable), death certificate or physician's notes. Each of these cases or families does not meet the operational diagnostic criteria for CS (Table 1). Further, they must minimally have at least one member with nonmedullary thyroid carcinoma and at least one other related member with breast cancer diagnosed at any age. They could also comprise single cases with both nonmedullary thyroid tumor and breast cancer. Among these 70 families/individuals, 1 germline PTEN mutation, c.209T->C (exon 3), was detected 13 (unpublished data). This was detected in a family where the proband was diagnosed with follicular thyroid carcinoma at the age of 31 and his mother had breast carcinoma diagnosed at 49 and 53, respectively, and endometrial carcinoma at 63. Half of these families/individuals were heterozygous at IVS8+32T/G thus excluding whole gene deletion. We and others have also shown that in CS and even BRR, whole gene deletion is rare 5,7,9,11,14,15. Indeed, if PTEN is grossly deleted, only the BRR phenotype results 11. Therefore, for the moment, the PI has decided that further hemizygote analysis on the large scale is not cost-efficient nor scientifically warranted.

From this Year 1 analysis, it would appear that the endometrial cancer feature in CS-like cases and families might increase the likelihood of finding a germline PTEN mutation. Therefore, while accrual of further CS-like families will continue, the PI will target families with endometrial pathology for Years 2 and 3. Southern analysis must await further accrual as amount of DNA per sample is limited with much of the analyses of these first 70 occurring off DNA templates extracted from paraffin-embedded archival material. Although promoter analysis was proposed in the original SOW, the promoter is within a 250 kb segment. We and others are trying to determine if the true promoter may be within a more confined region before beginning genetic analyses – this strategy would be meaningful.
Key Research Accomplishments

Task 1
- Clinical-genetic database being set up

Task 2
- Clinical-genetic database of CS-like families being set up
- Delineate the frequency of occult germline PTEN mutation in CS-like families and individuals
- Discovered that based on molecular data, the clinical operational diagnostic criteria for classic CS is robust
- Based on the findings thus far, the PI as Chair of the International Cowden Consortium has recommended that endometrial carcinoma be added to the list of major criteria in the operational diagnosis of CS (see Table 1 for 1995 Criteria). This is the first data-based update of criteria since 1995. The US NCCN/Genetic-High Risk Panel has agreed to adopt this revision in their 2000 guidelines.

Reportable Outcomes

Conclusions

In Year 1 of the grant, the PI has continued to accrue non-CS families and individuals. A clinical-genetic database is actively being built. It is envisioned that this will be on-going for the next 2 years. Because of the PI’s disruptive move from Boston in the beginning of the year, the database assistant is just being hired (the PI herself was manually inputting and analyzing data). Nonetheless, in the first analysis of non-CS CS-like families and individuals, the PI has found approximately 1.5-2% with an occult germline PTEN mutation. Re-examination of the family has found that they have breast, thyroid and endometrial cancer and no other stigmata of CS. Thus, the PI preliminarily concludes that the Clinical Operational Criteria for CS Diagnosis proposed by the International Cowden Consortium is robust, and that perhaps, endometrial carcinoma should be added to the list of major criteria.

In order to confirm these early findings, the PI will continue to accrue such CS-like families and individuals but to enrich for endometrial cancer or non-neoplastic endometrial disease (eg young onset endometrial fibroids can be a feature of CS). Germline PTEN mutation analysis will be pursued and the promoter elucidated and finally examined for alterations.
References


Appendix

Germline PTEN mutations in Cowden syndrome-like families

Debbie J Marsh, Patricia L M Dahia, Stacey Caron, Jennifer B Kum, Ian M Frayling, Ian P M Tomlinson, Kevin S Hughes, Rosalind A Eeles, Shirley V Hodgson, Vicky A Murday, Richard Houlston, Charis Eng

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Abstract

Cowden syndrome (CS) or multiple hamartoma syndrome (MIM 158350) is an autosomal dominant disorder with an increased risk for breast and thyroid carcinoma. The diagnosis of CS, as operationally defined by the International Cowden Consortium, is made when a patient, or family, has a combination of pathognomonic major and/or minor criteria. The CS gene has recently been identified as PTEN, which maps at 10q23.3 and encodes a dual specificity phosphatase. PTEN appears to function as a tumour suppressor in CS, with between 13-80% of CS families harbouring germline nonsense, missense, and frameshift mutations predicted to disrupt normal PTEN function. To date, only a small number of tumour suppressor genes, including BRCA1, BRCA2, and p53, have been associated with familial breast or breast/ovarian cancer families. Given the involvement of PTEN in CS, we postulated that PTEN was a likely candidate to play a role in families with a "CS-like" phenotype, but not classical CS. To answer these questions, we gathered a series of patients from families who had features reminiscent of CS but did not meet the Consortium Criteria. Using a combination of denaturing gradient gel electrophoresis (DGGE), temporal temperature gel electrophoresis (TTGE), and sequence analysis, we screened 64 unrelated CS-like subjects for germline mutations in PTEN. A single male with follicular thyroid carcinoma from one of these 64 (2%) CS-like families harboured a germline point mutation, c.209T→C. This mutation occurred at the last nucleotide of exon 3 and within a region homologous to the cytoskeletal proteins tensin and auxilin. We conclude that germline PTEN mutations play a relatively minor role in CS-like families. In addition, our data would suggest that, for the most part, the strict International Cowden Consortium operational diagnostic criteria for CS are quite robust and should remain in place.

(J Med Genet 1998;35:881-885)

Keywords: PTEN; Cowden syndrome; breast; thyroid Breast and thyroid cancer are two frequently occurring neoplasms in the female population. Increased risks for both breast and thyroid cancer are prominent features of Cowden syndrome (CS). The hallmark phenotype of this inherited cancer syndrome is the presence of hamartomas, developmentally incorrect, benign, hyperplastic growths, in multiple organ systems including the skin, gastrointestinal tract, central nervous system, breast, and thyroid. Breast cancer will develop in 25-50% of women with CS and 3-10% of all CS patients will develop thyroid cancer. At present, only four tumour suppressor genes have been associated with familial breast cancer, BRCA1, BRCA2, p53, and PTEN. Initially thought to account for over 80% of hereditary breast cancer, germline mutations in BRCA1 and BRCA2 together are now thought to account for 25-50% of all familial breast cancer, thus opening up the possibility of other BRCAX genes. Along these lines, germline mutations in p53 are associated with 70% of cases of Li-Fraumeni syndrome, an autosomal dominant condition comprising breast cancer, brain tumours, sarcomas, and adrenocortical carcinomas. Recently, the CS susceptibility gene has been identified as the tumour suppressor gene PTEN, also known as MMAC1 and TEP1. In vitro and in vivo PTEN maps to 10q23.3 and encodes a 403 amino acid dual specificity phosphatase. Germline missense and truncating mutations have been reported in between 13-80% of patients with CS. It should be noted that while initial linkage studies of 12 families with CS was highly suggestive of a single locus for CS, a subsequent study proposes that genetic heterogeneity may exist in CS.

At the somatic level, PTEN has been shown to be mutated or deleted in a number of human malignancies, including sporadic breast, brain, prostate, and kidney cancer cell lines, as well as in a number of primary tumours including endometrial carcinomas, glioblastomas, malignant melanoma, and thyroid and breast tumours.

Given the role of PTEN in CS and the relatively large percentage of familial cases of breast cancer that are not caused by germline mutation of BRCA1, BRCA2, or p53, we sought to determine whether PTEN may be mutated in
Table 1  Phenotypic classification of CS-like families

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<td>Breast carcinoma/CS-like (eg trichilemmoma), no thyroid involvement</td>
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<tr>
<td>Thyroid carcinoma/CS-like, no breast involvement</td>
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![Figure 1](image)

Figure 1  DGGE detection of c.209T→G in the germline of a patient from a CS-like family. Control mutations from CS and BRR families are also included to display the sensitivity of this technique for the detection of PTEN mutations. Lane 1, wild type control (exon 5); lane 2, Y65H (exon 5); lane 3, 15V2-2A→G (exon 3); lane 4, c.209T→G (exon 3); lane 5, wild type control (amplificon 5I), representing the 3' half of exon 5; lane 6, Q87X (amplificon 5I); lane 7, c.347-351delACAT (amplificon 5I); lane 8, wild type control (amplificon 5II, representing the 3' half of exon 5); lane 9, G124R (amplificon 5II); lane 10, E157X (amplificon 5II); lane 11, wild type control (exon 7); lane 12, R233X (exon 7); lane 13, c.791ATins (exon 7).

DENATURING GRADIENT GEL ELECTROPHORESIS (DGGE) AND TEMPORAL TEMPERATURE GEL ELECTROPHORESIS (TTGE)

A combination of DGGE and TTGE was performed for all nine exons of PTEN. GC clamped primer sequences, PCR conditions, and DGGE conditions have been previously described, with the exception of primers for exons 2 and 4. Exon 2 and 4 primer sequences, with GC clamps added, were as follows: exon 2, 2F, 5'-CGT CCC GCC TTT GAT TGC TGG ATC TTT CAG-3' and 2R, 5'-CGC CCG CCG CCC GGC CCC GTG CCG CCG CCC CCC GGC GTT AAC ACA CAA CAT G-3'; exon 4, 4F, 5'-CGT CCC GCC CCG CCC CCG CCC GCC CCC GTG CCG CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC CCC 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SEQUENCE ANALYSIS
Exons which showed DGGE and TTGE variants underwent direct sequence analysis. The PCR primers and reaction conditions have been described elsewhere.\textsuperscript{14-16,18,20} PCR products were gel isolated and purified using the Wizard PCR Preps DNA Purification System (Promega, Madison, WI). Direct sequencing of these products was performed using the ABI Prism dye terminator cycle sequencing ready reaction kit (Perkin-Elmer Corp. Norwalk, CT). Cycle sequencing products were electrophoresed on 6% Long ranger gels (FMC Bioproducts, Rockland, ME) and analysed on an Applied Biosystems model 373A automated DNA sequencer (Perkin-Elmer Corp).

PTEN POLYMORPHISM ANALYSIS
A previously identified intronic polymorphic site in PTEN, IVS8+32G\textrightarrow{}T, was analysed in a single affected member from each CS-like family to investigate hemizygosity at the PTEN locus in mutation negative families. This site is moderately heterozygous, with an earlier report finding 50% of samples to be informative.\textsuperscript{26} Potential hemizygosity was assessed by the amplification of exon 8 and flanking intronic sequence and digestion with the restriction endonuclease HincII under conditions suggested by the manufacturer (New England Biolabs, Beverly, MA).

Results
PTEN MUTATION ANALYSIS
A missense point mutation, c.209T\textrightarrow{}C (L70P), predicted to affect splicing was identified in a single affected patient (1 of 64, 2%) (fig 1). This mutation was not identified in 100 normal alleles. When this occult germ line PTEN mutation was identified, the family history was reassessed (fig 2). The subject analysed for this study, III.1, developed follicular thyroid carcinoma at the age of 31. His mother, II.2, had breast adenocarcinoma diagnosed at the age of 49 and again at 53. She also had endometrial carcinoma diagnosed at 63 years. Careful clinical assessment of these two subjects was unable to identify macrocephaly, skin lesions typical of CS, or scrotal tongue. The maternal grandfather, I.1, was diagnosed with leukaemia at the age of 57. Unfortunately, family members other than III.1 were unavailable for analysis. Fresh tumour from III.1, which would have allowed us to study the putative aberrant splicing effect of this mutation, was also unavailable. No mutations were identified in the other 63 unrelated CS-like families.

PTEN POLYMORPHISM ANALYSIS
Forty-eight percent (30 of 63) of unrelated subjects from PTEN mutation negative CS-like families were found to be heterozygous at the IVS8+32T/G site. This analysis would suggest that, at least in these families, gross germ line deletion of PTEN can be excluded.

Discussion
An occult germline PTEN mutation, c.209T\textrightarrow{}C at the last nucleotide of exon 3 was found in one of 64 (2%) CS-like families. This family's cancers, comprising leukaemia, which may or may not be related, adenocarcinoma of the breast, endometrial carcinoma, and follicular thyroid carcinoma, together do not meet the International Cowden Consortium Criteria used for the diagnosis of CS in this study. However, we cannot exclude the possibility that this family represents a case of low penetrance CS. The family with PTEN mutation in this study contrasts with that in a recent study that reported a PTEN mutation in a family initially classified as having breast and thyroid tumours only but reclassified as CS after mutation analysis led to closer clinical assessment.\textsuperscript{36} Closer clinical assessment of the family presented in the current study did not identify additional features of CS.

In the remaining families where no occult germline mutations were identified, it is highly unlikely that these mutations would have gone undetected. Both DGGE and TTGE are highly sensitive mutation detection techniques\textsuperscript{37} and both have been shown consistently to detect known PTEN mutations and other sequence polymorphisms (Marsh and Eng, unpublished data, 1998; fig 1). Further, because at least one affected member from nearly half of these mutation negative families was heterozygous at the IVS8+32T/G polymorphism, whole gene deletion is unlikely, at least in these families.

In CS, while missense and truncating mutations are scattered largely along the entirety of PTEN, a mutational "hot spot" exists in exon 5, which contains the PTPase core motif at codons 122-132.\textsuperscript{16-18} Thus, many mutations in CS are predicted to disrupt the phosphatase function of this protein. Interestingly, the mutation identified in exon 3 falls in the N-terminal half of the PTEN protein that has been shown to have some sequence similarities to the cytoskeletal proteins tensin and auxilin.
Specifically, the leucine residue at codon 70 that is altered by this T to C point mutation (L70P) is conserved in both bovine auxilin and chicken tensin. Thus, it is possible that this mutation may be affecting the phosphatase function of this protein, as one may predict if this putative splice-site mutation leads to a truncated protein, and may also function to disrupt normal cellular motility and cell-cell interactions.

Whether germline PTEN mutations are associated with CS and related inherited hamartoma syndromes (Bannayan-Ruvalcaba-Riley syndrome, BRR, MIM 153480) and juvenile polyposis syndrome (JPS, MIM 174900), as well as syndromes comprising partial CS phenotypes, is largely unknown. Before the identification of PTEN as the CS gene, it was not inconceivable that the three related hamartoma syndromes and CS-like syndromes were all associated with different mutations in a single gene. We have shown that germline PTEN mutations are associated with the great majority, approximately 80%, of classical CS families. Nelen et al. identified PTEN mutations in 47% of CS cases studied. One other study of 25 CS families identified only 13% of families with germline PTEN mutation. This was perhaps not surprising as limited linkage information in these families suggested the possibility of genetic heterogeneity in CS, even though initial studies of a group of 12 CS families showed no evidence for heterogeneity.

We have also shown that germline PTEN mutations account for at least a proportion of BRR, which is characterised by macrocephaly, lipomatosis, thyroid dysfunction, hamartoma-tous polyps of the gastrointestinal tract, and pigmented macules of the glans penis, but without a known predisposition to breast and thyroid cancer. How mutations in a single gene, at times identical, can function to predispose to two overlapping but apparently distinct syndromes, one with malignancy and one without, remains to be elucidated.

Disparate reports concerning the third hamartoma syndrome, JPS, and PTEN mutation or deletion have recently been published. A putative JPS locus, JPH, at 10q22-24 was initially thought to encompass PTEN, although fine structure mapping placed this locus slightly centromeric of PTEN. Subsequently, the 10q22-24 region was excluded as a putative JPS locus by linkage analysis in eight JPS families. Screening of PTEN in 21 classical JPS families and 16 cases of sporadic JPS did not identify any germline mutations. In contrast, PTEN mutation has been reported in four patients with "juvenile polyposis" although the clinical diagnosis of classic juvenile polyposis in these cases is questionable. Given these genetic data and the phenotypic overlap of these syndromes, we can say with some confidence that if a germline PTEN mutation were detected in a person previously thought to have "juvenile polyposis", then the diagnosis needs to be revised, as that person is likely to have either CS or BRR.

Along the same lines, we have now investigated a cohort of families, each of which contains some of the component tumours of CS but do not meet the Consortia diagnostic criteria for CS. Only one such family was found to have an occult germline PTEN mutation, arguing that such germline alterations play a minor role in families that do not meet the strict CS diagnostic criteria. Nonetheless, this finding is significant for three reasons. Firstly, it suggests that the operational diagnostic criteria for CS established by the International Cowden Consortium are, for the most part, robust and are useful for identifying PTEN mutation positive CS families. Secondly, we must also conclude from our data that other genes are involved which lend susceptibility to a CS-like disease and to site specific breast and non-medullary thyroid cancer. Thirdly, for non-CS subjects identified with occult PTEN mutations, albeit uncommonly, there are important implications for future hamartoma/cancer development that should impact on surveillance.

Unanswered questions remain, however. For example, are CS-like families without germline PTEN mutations at any less risk of cancer than those with mutations? Preliminary genotype-phenotype analyses suggest that classical CS families without germline PTEN mutations are at lower risk of developing malignant breast disease compared to their PTEN mutation positive counterparts. By extrapolation, it would seem that PTEN mutation negative CS-like families should be at decreased risk of developing breast cancer. Unfortunately, this study was unable to confirm this clinically relevant extrapolation. We can conclude, however, that in the majority of cases, germline PTEN mutations lead specifically to a CS or BRR phenotype and that the phenotype of CS-like families is, for the most part, caused by unknown mechanisms.

We would like to thank the patients and families who participated in this study, and Dr Oliver Glime for critical reading of this manuscript. Ms Elaine Kreelorn is acknowledged for assistance with the patients. The Molecular Biology Core Facility at the Dana-Farber Cancer Institute, Boston, is acknowledged for running sequencing gels. This study was supported by the Susan G. Komen Breast Cancer Foundation (to PLMD and CE), the American Cancer Society (RPG 97-064-02VM), the Barr Investigatorship, and a Breast Cancer Research Grant (34088PP10099) from the Massachusetts Department of Public Health (to CE). CE is the Lawrence and Susan Marx Investigator in Human Cancer Genetics.

10 Eng C. From bench to bedside... but when? Genome Res 1997;7:669-72.
CURRICULUM VITAE

Date Prepared: Sept 29, 1999

Name: Charis Eu Li ENG

Office Address: Human Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, 690C Medical Research Facility, 420 West 12th Avenue, Columbus, OH 43210, USA

Home Address: 1683 Quarry Trace, Columbus, OH 43204, USA

Place of Birth: Republic of Singapore

Education:
1982 BA University of Chicago, Chicago, IL (Biological Sciences with Honors)
1986 PhD University of Chicago, Chicago, IL (Developmental Biology)
1988 MD University of Chicago, Chicago, IL (Medicine)

Postdoctoral Training:

Internship and Residency:
1988-89 Intern, Internal Medicine, Beth Israel Hospital, Boston, MA
1989-90 Junior Assistant Resident, Internal Medicine, Beth Israel Hospital, Boston, MA
1990-91 Senior Assistant Resident, Internal Medicine, Beth Israel Hospital, Boston, MA

Fellowships:
1988-93 Clinical Fellow in Medicine, Harvard Medical School, Boston, MA
1991-94 Clinical Fellow, Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
1991-92 Clinical Fellow, Division of Medical Oncology, Brigham and Women's Hospital, Boston, MA
1992-95 Cancer Research Campaign - Dana-Farber Cancer Institute Fellow in Human Cancer Genetics, University of Cambridge, UK
1992-95 Research Fellow, Department of Pathology, University of Cambridge, UK

Licensure and Certification:
1990 Commonwealth of Massachusetts Medical Licensure, No. 72073
1991 American Board of Internal Medicine, Specialty Board Certification in General Internal Medicine, No. 135435
1992-95 Limited Registration, No. 92/3382, General Medical Council, London, UK
1997 American Board of Internal Medicine, Subspecialty Board Certification in Medical Oncology
119. State of Ohio Medical Licensure
Academic Appointments

1994-95  Instructor in Medicine, Harvard Medical School, Boston, MA  
1995-98  Assistant Professor of Medicine, Harvard Medical School, Boston, MA  
1999-    Associate Professor of Medicine and Human Cancer Genetics, Ohio State University, Columbus, OH

Hospital or Affiliated Institution Appointments:

1992-95  Honorary Clinical Fellow/Senior Registrar, Clinical Cancer Genetics, Department of Clinical Genetics, Addenbrooke’s Hospital, Cambridge, UK  
1993-94  Honorary Clinical Status in Clinical Cancer Genetics, The Royal Marsden Hospital, London and Sutton, UK  
1994-95  Honorary Consultant in Clinical Cancer Genetics, The Royal Marsden Hospital, London and Sutton, UK  
1995-98  Active Staff Physician, Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA  
1995-98  Associate Physician, Division of Medical Oncology, Department of Medicine, Brigham and Women’s Hospital, Boston, MA  
1999-    Director, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH  
1999-    Member, Molecular Biology and Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University, Columbus, OH

Other Professional Positions and Major Visiting Appointments

1994-95  Member, Emmanuel College, Cambridge, UK  
1995-    Honorary Member, Emmanuel College, Cambridge, UK  
1995    Consultant to the Molecular Genetics Laboratory, Albert Ludwigs-Universität Freiburg, Abteilung Innere Medizin IV - Nephrologie, Freiburg, Germany, July 17-19  
1995-    Honorary Fellow, CRC Human Cancer Genetics Research Group, University of Cambridge, UK

Hospital and Health Care Organisation Clinical Responsibilities:

1995-98  Staff Medical Oncologist, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Boston, MA  
1995-98  Staff Clinical Cancer Geneticist, Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute, Boston, MA  
1995-96  Staff Medical Oncologist, Head and Neck Clinic, Dana-Farber Cancer Institute, Boston, MA  
1997-98  Staff Medical Oncologist, Endocrine Cancer Clinic, Dana-Farber Partners Cancer Center, Boston, MA  
1999-    Director and Attending Clinical Cancer Geneticist, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH
Major Administrative Responsibilities:

1996-99 Coordinator, Harvard Longwood Seminars in the Genetics of Cancer and Aging, Dana-Farber Partners Cancer Center, Boston, MA
1999- Director, Clinical Cancer Genetics Program, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH
Major Committee Assignments:

**Medical School**

1983-86
Interviewer for first year applicants to the Pritzker School of Medicine, University of Chicago, IL

1999-
Alternate Member, Biomedical Human Protection Committee, Ohio State University, Columbus, OH

**Hospital**

1995
Scientific Steering Subcommittee, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Boston, MA

1996-98
Molecular Diagnostics Committee of the Clinical Cancer Genetics Program, Dana-Farber Partners Cancer Care, Boston, MA

1996
High Risk Committee, Gastrointestinal Cancer Center, Dana-Farber Partners Cancer Care, Boston, MA

1996-98
Steering Committee, Endocrine Cancer Clinic, Dana-Farber Partners Cancer Center, Boston, MA

1997-98
Steering Committee, Gastrointestinal Cancer Center, Dana-Farber Partners Cancer Center, Boston, MA

1997-98
Human Cancer Genetics Working Group, Dana-Farber Partners Cancer Center, Boston, MA

1999-
Clinical Trials Office Steering Committee, James Cancer Hospital and Solove Research Institute and Comprehensive Cancer Center, Ohio State University, Columbus, OH

1999-
Clinical Scientific Research Committee, James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, Ohio State University, Columbus, OH

**National**

1996-
Reviewer, Department of Veterans Affairs Merit Review Applications

1997-98
Reviewer and Expert Consultant, American Society of Clinical Oncology Task Force on Cancer Genetics Education

1998-
Reviewer, Molecular Biology 3 Study Section, Department of Defence US Army Research Medical and Material Command Breast Cancer Research Program

1999
Reviewer, Susan G. Komen Breast Cancer Research Foundation Grants

1999
Site Visit Team Member, Quadriannual Site Visit, National Institute of Child Health and Development, Developmental Endocrinology Branch

1999
Reviewer, Cancer Genetics Section, American Society of Human Genetics Annual Meeting Abstracts

1999-
National Comprehensive Cancer Network (NCCN) Guidelines Panel Member: Genetics/Familial High Risk Screening Guidelines

**International**

1994-
Coordinator and co-chair, International RET Mutation Consortium

1994-
Coordinator and chair, International Cowden Syndrome Consortium

1995-98
International Review Board, Dutch Cancer Society

1997
Ad Hoc Review Committee, Programme Project Grant, National Cancer Institute of Canada
1997- Peer Review Panel, Project Grants, Comitato Promotore Telethon, Italy
1997- Reviewer and Full Member, National Cancer Institute of Canada, Panel J: Pathology, Tumor Markers, Molecular Epidemiology and Clinical Correlative Studies, Toronto, ON
1998- Ad Hoc External Reviewer, Italian Association for Cancer Research
1998- Member, Steering Committee, Breast Cancer Information Core (BIC)
1999- Member, International Scientific Committee, 8th International Workshop on Multiple Endocrine Neoplasia, Jerusalem, Israel, May 2001

Professional Societies and Colleges:

1982- Phi Beta Kappa, Member
1982-87 Sigma Xi, Associate Member
1982-88 American Medical Students' Association, Member
1982-88 American Medical Association, Member
1982-89 American Medical Women's Association, Member
1984-88 American Association for the Advancement of Science, Member
1984-89 New York Academy of Sciences, Member
1987- Sigma Xi, Member
1988- Alpha Omega Alpha, Member
1989-92 American College of Physicians, Associate
1990-98 Massachusetts Medical Society, Member
1992-99 American College of Physicians, Member
1995- New York Academy of Sciences, Member
1996- American Society of Clinical Oncology, Member
1996- American Society of Human Genetics, Member
1998- American Association for Cancer Research, Member
1999- American College of Physicians, Fellow

Editorial Boards:

1998- Journal of Medical Genetics, North American Editor
1998- Journal of Medical Genetics, Associate Editor for Cancer Genetics
1998- Journal of Endocrine Genetics, Editorial Board Member

Ad hoc Reviewer for:

1998- American Journal of Human Genetics
1997- American Journal of Pathology
1997- American Journal of Surgical Pathology
1999- BioTechniques
1997- Blood
1998- British Journal of Cancer
1998- Cancer
1996- Cancer Epidemiology, Biomarkers and Prevention
1997- Cancer Research
1997- Carcinogenesis
1998- Clinical Cancer Research
1995- Clinical Endocrinology
1995- Clinical Genetics
1996- European Journal of Endocrinology
1997- European Journal of Human Genetics
1997- Experimental Cell Research
1996- Gastroenterology
1995- Genes, Chromosomes and Cancer
1998- Genomics
1997- Human Genetics
1994- Human Molecular Genetics
1994- Human Mutation
1998- International Journal of Cancer
1996- Journal of the American Medical Association
1995- Journal of Clinical Endocrinology and Metabolism
1999- Journal of Experimental Medicine
1999- Journal of Clinical Investigation
1995- Journal of Clinical Oncology
1994-98 Journal of Medical Genetics
1998- Journal of the National Cancer Institute
1996- Mutation Research
1995- Nature Genetics
1996- New England Journal of Medicine
1995- Oncogene
1997- Proceedings of the National Academy of Sciences, USA

Awards and Honors:

1978-82 Dean's List, College, University of Chicago, IL
1981 Edmondson Summer Research Fellowship, University of Chicago, IL
1981-82 Yim Chan Merit Scholarship, University of Chicago, IL
1982 Graduation with Divisional and Collegiate Honors, University of Chicago, IL
1982 Phi Beta Kappa
1982 Sigma Xi, Associate Membership
1982 Sigma Xi Science Prize Competition, Honorable Mention, University of Chicago, IL
1982 Sigma Xi Certificate of Merit for Excellence in Undergraduate Scientific Research, University of Chicago, IL
1982-83 Dean's Letter of Commendation for Excellence in Gross Anatomy and Microbiology, Pritzker School of Medicine, University of Chicago, IL
1982-84 Far East Scholarship, Pritzker School of Medicine, University of Chicago, IL
1983 National Institutes of Health Summer Research Fellowship, Pritzker School of Medicine, University of Chicago, IL
1984-86 American Heart Association - Borg-Warner Medical Student Research Fellowship, University of Chicago, IL
1987 Sigma Xi, promotion to Full Membership
1988 Alpha Omega Alpha
1990 Nomination for Chief Residency, Department of Medicine, Beth Israel Hospital, Boston, for 1992-93 (Position Declined)
1990  Nomination for the National Institutes of Health-Upjohn Medical Residents Research Award
1991  Upjohn Travel Award to the Meeting of the American Association for Cancer Research, Houston, TX
1992  Johanna Wood Fellowship, Dana-Farber Cancer Institute, Boston, MA
1992-95  Cancer Research Campaign - Dana-Farber Cancer Institute Fellowship in Human Cancer Genetics, University of Cambridge, U.K.
1995-97  Lucille P. Markey Charitable Trust Young Scientist Award
1995-98  The First Lawrence and Susan Marx Investigatorship in Human Cancer Genetics, Dana-Farber Cancer Institute, Boston, MA
1996  Patterson Fellowship, Dana-Farber Cancer Institute, Boston, MA
1997-99  Barr Investigatorship, Dana-Farber Cancer Institute, Boston, MA
1999  International Scientific Committee, 8th International Workshop on Multiple Endocrine Neoplasia, Jerusalem, Israel, May, 2001
Laboratory and Clinical Investigator Track

A. Report of Research

1. Major research interests:

   1. Cancer Genetics
   2. Molecular Epidemiology of Cancer
   3. Second Malignancies in Retinoblastoma Patients
   4. Genetics of Multiple Endocrine Neoplasia Type 2 and Related Cancers
   5. Familial Gastrointestinal Cancers
   6. Cowden Syndrome and Related Cancers
   7. Inherited Hamartoma-Neoplasia Syndromes

2. Narrative description of research

   The broad thrust of my laboratory involves the utilisation of DNA-based methods to
   identify and characterise genes which cause susceptibility to inherited cancer syndromes, to
   determine their role in sporadic carcinogenesis and to perform molecular epidemiologic analyses as
   they might relate to future clinical applications. Upon this framework, we are examining the
   genetics of two inherited thyroid cancer syndromes, Cowden syndrome (nonmedullary thyroid
   cancer) and MEN 2 (medullary thyroid cancer), and related sporadic cancers. Hence, the genetics
   of susceptibility gene PTEN, encoding a dual specificity phosphatase on 10q23.3, is being
   examined in Cowden syndrome and other inherited hamartoma syndromes as well as populations
   of isolated breast and thyroid cancer cases. Somatic genetics of PTEN is being pursued in a range
   of sporadic cancers including sporadic counterpart Cowden component tumors, breast, thyroid and
   endometrial carcinomas. Gene-gene interactions and gene-environment interactions are beginning
   to be explored. Biochemical, cellular and functional studies are beginning to be performed in our
   laboratory as well as in collaboration with a number of laboratories locally, nationally and
   internationally. The genetics of the RET proto-oncogene are pursued for clinical translational
   purposes for MEN 2 and sporadic neuroendocrine tumors. Towards those ends, genotype-
   phenotype analyses and genotype-prognosis analyses are being performed. Examination of
   common low penetrance variants in sporadic medullary thyroid carcinoma is also being pursued in
   the hope of identifying common alleles for predisposition in sporadic neuroendocrine tumors.

   Recent efforts in my laboratory have focused on the role of the nuclear receptor
   transcription factor PPARγ in sporadic carcinogenesis. Troglitazone (Rezulin™), which is a
   specific synthetic ligand for PPARγ, is an oral hypoglycemic agent used by over 1.6 million
   Americans. So, our work may have broad implications not only for examining the pathogenesis of
   common cancers but may impact public health as well. This avenue of investigation also promises
   direct translation into clinical oncologic practice.

3. Research funding information:

   1981     Edmondson Summer Research Fellowship, University of Chicago     PI
             (Advisor: Edward D. Garber)
   1978-82  Yim Chan Merit Scholarship, University of Chicago, IL
   1984-86  American Heart Association Borg-Warner Medical Student Research
             Fellowship, University of Chicago Pritzker School of Medicine, IL     PI
   1992-95  Cancer Research Campaign [CRC] Dana-Farber Fellowship     PI
Integrated fellowship in clinical cancer genetics and molecular cancer genetics at the University of Cambridge, UK
(Advisor: Bruce A. J. Ponder)

1995-97 New Investigator Award, Charles A. Dana Foundation

1995-97 New Investigator Award, Markey Charitable Trust

1995-98 Lawrence and Susan Marx Investigatorship in Human Cancer Genetics PI

1996 Patterson Fellowship PI

1996-98 Harvard Nathan Shock Center Award for the Basic Biology of Aging, NIA
State of the art resource core for two dimensional gene scanning

1996-99 Barr Investigatorship PI
Human cancer genetics research

1997-98 Women's Cancer Program Grant, Dana-Farber Partners Cancer Center
Development of a rapid multi-gene test for hereditary breast cancer PI

1997-99 American Cancer Society (National) Research Project Grant PI
Isolation and characterisation of Cowden syndrome gene

1997-1999 DFG Training Fellowship (Germany) Mentor
Trainee PI: Oliver Gimm, MD
Novel mutations and low penetrance alleles in the RET proto-oncogene in multiple endocrine neoplasia type 2 and sporadic medullary thyroid carcinoma

1997-2000 Susan G. Komen Breast Cancer Foundation Postdoctoral Fellowship PI
Trainee: Patricia L M Dahia, MD, PhD
Role of Cowden susceptibility gene in breast cancer

1998 Breast Cancer Research Award, Massachusetts Department of Public Health PI
*PTEN*, the Cowden disease gene, in patients and families with breast cancer and thyroid disease

1998-99 ASCO Young Investigator Award Mentor
Prognostic markers for progression of esophageal adenocarcinoma
Trainee PI: Matthew H. Kulke, MD

1998-1999 Concert for the Cure Breast Cancer Research Award PI
Genetics of *PTEN* in Cowden syndrome and unselected breast cancer patients

1999 Ohio State University Seed Grant PI
Mapping the susceptibility gene for hereditary and sporadic Barrett esophagus and esophageal adenocarcinoma

Genetics of *PTEN* in different forms of hereditary breast cancer

1998-2001 American Cancer Society (National) Research Project Grant PI
Genetics of *PTEN* in Cowden syndrome and sporadic breast cancer
1999-2002 National Institutes of Health Workstatement (RFP)
A phase 2 study of a selective estrogen receptor modulator (LY353381) vs.
Tamoxifen vs. placebo in premenopausal women with an increased risk for breast
cancer

1999-2001 Mary Kay Ash Charitable Foundation Grant
Genetic and functional analysis of PPAR-gamma as a novel tumor suppressor locus
in sporadic breast carcinoma
### B. Report of Teaching

#### Local Contributions

**Medical School / School of Public Health**

<table>
<thead>
<tr>
<th>Year</th>
<th>Course/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Medical Genetics, Teaching Assistant for 100-110 second year medical students, University of Chicago Pritzker School of Medicine (Contact 5 hr/wk, Prep 5 hr/wk)</td>
</tr>
<tr>
<td>1996-98</td>
<td>Molecular Epidemiology, Guest Lecturer for 30-50 medical, dental and graduate students, medical fellows and instructors, Harvard School of Public Health (Contact 1-2 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>HMS211A Graduate Course in Biochemistry and Cell Biology, invited lecture on inherited cancer syndromes for 20 graduate, dental and medical students, Harvard Medical School, Boston: (Contact 1.5 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1998</td>
<td>Harvard Medical School Course in Genetics, Embryology and Reproduction, Tutor for group of 7-10 medical students (Contact 40 hr, Prep 20 hr)</td>
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</table>

**Graduate Medical Course/Seminar/Invited Teaching Presentation**

<table>
<thead>
<tr>
<th>Year</th>
<th>Course/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Grand Rounds, Beth Israel Hospital, Boston: Causes of late mortality in retinoblastoma patients, invited speaker (Contact 20 min, Prep 3 hr)</td>
</tr>
<tr>
<td>1994</td>
<td>Department of Medicine Seminar Series, University of Cambridge School of Clinical Medicine: The many faces of RET, invited lecture for 50 housestaff and faculty of the Clinical School (Contact 1 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1996</td>
<td>Seminars in Medicine of the Beth Israel Hospital: From bench to bedside: the RET proto-oncogene in multiple endocrine neoplasia, invited lecture for 30-60 faculty and trainees from the Boston area (Contact 1.5 hr, Prep 3 hr)</td>
</tr>
<tr>
<td>1996</td>
<td>Harvard Medical School Department of Genetics Seminar: The polygenic etiology of Hirschsprung disease, invited speaker for 20-25 clinical genetics fellows, postdoctoral fellows and genetics faculty (Contact 1 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>Brigham and Women's Hospital Specialty Lecture for Medical Housestaff: Genetics of endocrine tumors, invited speaker for 50-60 medical housestaff (Contact 1 hr, Prep 1 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>Massachusetts Cancer Center Seminar, Charlestown, MA: RET, GDNF and GDNFR-α in MEN 2, invited speaker for 30-50 PI's, postdoctoral fellows and graduate students (Contact 1.5 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>GI Grand Rounds, Massachusetts General Hospital: Molecular genetics of Hirschsprung disease for 15-25 GI fellows and faculty (Contact 1 hr, Prep 2 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>Women's Cancer Program, Dana-Farber Partners Cancer Center, Boston: Identification of the Cowden syndrome susceptibility gene, invited speaker for 20-30 multidisciplinary faculty, clinical fellows, housestaff, postdoctoral fellows, graduate students (Contact 1 hr, Prep 1 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>Breast Center Basic Biology Seminar, Dana-Farber Partners Cancer Center, Boston: Identification of the Cowden syndrome gene, a multipurpose gene which predisposes to breast and thyroid cancers, invited speaker for 40-60 multidisciplinary faculty, fellows and housestaff (Contact 1 hr, Prep 1 hr)</td>
</tr>
<tr>
<td>1997</td>
<td>Harvard-Longwood Seminars in the Genetics of Cancer and Aging, Boston: PTEN in inherited hamartoma-cancer syndromes: one gene-many syndromes? Invited speaker for 50-70 clinical and basic science faculty, postdoctoral fellows, clinical fellows, and graduate students from the Harvard Longwood area (Contact 1 hr, Prep 1 hr)</td>
</tr>
</tbody>
</table>
1997 Massachusetts General Hospital Cancer Center Grand Rounds, Boston: PTEN in Cowden syndrome and sporadic breast and thyroid cancers (Contact 1 hr, Prep 1 hr)
1999 Ohio State University Human Cancer Genetics Program Seminar, Columbus, OH: PTEN and the great imitator: Cowden syndrome (Contact 1 hr, Prep 1 hr)

Continuing Medical Education Course
1997 Cancer Genetics for Office Practice: Genetics of thyroid cancer in everyday practice, faculty (Contact 3 hr, Prep 1 hr)
1997 American College of Surgeons, Massachusetts Chapter, Waltham: Genetics of colorectal tumors, faculty (Contact 2 hr, prep 1 hr)
1998 Massachusetts Eye and Ear Infirmary and Harvard Medical School Course on Thyroid and Parathyroid Tumors: RET and medullary thyroid carcinoma, faculty (Contact 30 min, prep 20 min)

Advisory and Supervisory Responsibilities
1988-89 Teaching and supervision of Harvard medical students during clinical clerkship, Beth Israel Hospital, 1 medical student per rotation (200 hr/yr)
1989-91 Teaching and supervision of Harvard medical students during clinical clerkship and medical interns, Beth Israel Hospital, 2-4 interns +/- 1 medical student per rotation (2000 hr/yr)
1991-92 Teaching and supervision of medical students, and medical housestaff from Brigham and Women's Hospital and Beth Israel Hospital, 3-8 housestaff +/- 1 medical student per month (500 hr/yr)
1993-95 Teaching and supervision of technicians, students and junior postdoctoral fellows, CRC Human Cancer Genetics Research Group, Department of Pathology, University of Cambridge, 2 technicians, 0-3 medical/graduate students and 0-1 junior postdoctoral fellow (20 hr/wk)
1995- Teaching and supervision of postdoctoral fellows, students and technicians working in my laboratory, 2-6 postdoctoral fellows, 0-1 medical students, 1-3 technicians (15 hr/wk)
1996-98 Teaching and supervision of medical oncology and genetics fellows and genetics counsellors, Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute (3-5 hr/wk)
1996-98 Clinic Attending for medical oncology fellows, Dana-Farber Cancer Institute, 1-6 fellows per session (5-10 hr/mth)
1999- Direction and administration of the Clinical Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University: 1.5-2 MD attending clinical cancer geneticists, 0-1 oncology fellow, 0-1 medical resident, 3-4 cancer genetics counselors, 0-1 research assistant, 1 data manager and 2 executive support associates (20 hr/wk)

Laboratory-Based Trainees

Postdoctoral Trainees
Debbie J. Marsh, PhD 1996-99
Project: Genetics of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome
Current Position: Lecturer, Dept of Medicine, University of Sydney School of Medicine, Sydney, Australia

Matthew H. Kulke, MD 1997-99
Project: Molecular epidemiology and prognostic markers in sporadic gastrointestinal cancers
Current Position: Instructor in Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Patricia L.M. Dahia, MD, PhD 1997-
Project: Somatic genetics and biochemical expression of PTEN in sporadic tumors
Current Position: Postdoctoral Senior Research Associate, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Instructor in Medicine, Harvard Medical School

Oliver Gimm, MD 1997-
Project: Genetics of neuroendocrine tumors
Current Position: DFG Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Aurel Perren, MD 1998
Project: Immunocytochemistry of PTEN in sporadic tumors of the breast and thyroid
Current Position: Resident in Pathology, University of Zürich School of Medicine, Zürich, Switzerland

Jen Jen Yeh, MD 1998-99
Project: Somatic genetics of non-medullary thyroid carcinomas and the role of the mitochondrial genome
Current Position: Postdoctoral Research Fellow, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Liang-Ping Weng, MD, MS 1998-
Project: Biochemistry and cell biology of PTEN in breast and thyroid carcinogenesis
Current Position: Research Scientist, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Xiao-Ping Zhou, MD, PhD 1998-
Project: Genetics of central nervous system tumors
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Ravshan Burikhanov, PhD 1999-
Project: Cell biology of RET, PTEN and PPARgamma in thyroid cancer models
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University, Columbus, OH

Keisuke Kurose, MD, PhD 1999-
Project: Genetics of PTEN and PPARgamma in gynecologic cancers
Current Position: Postdoctoral Researcher, Human Cancer Genetics Program, Ohio State University Columbus, OH

Student Trainees

Antje Gössling 1996
Project: Genetics of GDNF and GFRalpha-1 in central nervous system tumors
Current Position: Resident in Clinical Genetics, Faculty of Medicine, University of Tübingen School of Medicine, Germany
Eva-Maria Dürr
Project: Genetics of CUL2 and VBP-1 in phaeochromocytomas
Current Position: Senior Medical Student, University of Bonn School of Medicine, Germany

Ying Huang
Project: Mapping the susceptibility gene for familial nonmedullary thyroid cancer
Role: PhD thesis committee member (Albert de la Chapelle, MD, PhD, Advisor and Chair)

Junior Faculty Mentored
Matthew H. Kulke, MD  Instructor in Medicine, Dana-Farber Cancer Institute
ASCO Young Investigator Award  1998-99

Kornelia Polyak, MD, PhD  Assistant Professor of Medicine, Dana-Farber Cancer Institute
ASCO Career Development Award  1999-2003

Patricia L M Dahia, MD, PhD  Instructor in Medicine, Dana-Farber Cancer Institute  1999-

Liang-Ping Weng, MD, MS  Research Scientist, Ohio State University  1999-

Leadership Role
1995-99  Director, Harvard Longwood Seminars in the Genetics of Cancer and Aging, organisation and coordination of seminar topic and speakers, invitation of speakers, and public relations for the seminar (CME 1 course)
1999- Director, Clinical Cancer Genetics Program, Comprehensive Cancer Center, Ohio State University

Regional, National and International Contributions (Invited Presentations)

1993  Lancet Grand Round: Familial Cancer Syndromes. Case Presentations and Multiple Endocrine Neoplasia Type 2A, Royal Marsden Hospital, Sutton

1993  ICRF Department of Medical Oncology Seminar, St. Bartholomew's Hospital, London: The multiple endocrine neoplasia type 2 syndromes

1994  Faculty, March of Dimes 25th Clinical Genetics Conference, Orlando, FL, USA Symposium in Genetics and Development: The molecular genetics of multiple endocrine neoplasia type 2

1994  Arbeitsgemeinschaft für Gynäkologische Onkologie, Vienna, Austria: The familial and genetic risks of ovarian cancer

1994  Postgraduate Training Course in Endocrinology: Multiple Endocrine Neoplasia Type 2. British Society for Endocrinology, St. Mary's Hospital, London, UK

1994  Symposium on Genotype-Phenotype Correlations, British Medical Genetics Conference, York, UK: Mutations of the RET proto-oncogene in the multiple endocrine neoplasia type 2 syndromes and Hirschsprung disease

1995  Case Presentation Conference, Department of Medical Genetics, BC Children's Hospital, University of British Columbia, Vancouver: The role of the RET proto-oncogene in the multiple endocrine neoplasia type 2 syndromes and Hirschsprung disease

1995  Meeting of the Clinical Molecular Genetics Society, Selwyn College, Cambridge: Mutational analysis of the RET proto-oncogene in MEN 2
1995  Department of Internal Medicine IV - Nephrology Special Seminar, Albert
Ludwigs University of Freiburg, Germany: Phaeochromocytoma and
multiple endocrine neoplasia type 2: molecular genetic analysis

1995  EORTC Thyroid Group Meeting, London, UK: Germline mutations in the
RET proto-oncogene in the multiple endocrine neoplasia type 2 syndromes

1995  Wessex Regional Genetics Laboratory Seminar, Salisbury, UK: The many
faces of RET: multiple endocrine neoplasia type 2 and Hirschsprung disease

1996  Journées Internationales H P Klotz d’Endocrinologie Clinique, Paris,
France: RET mutations in multiple endocrine neoplasia type 2 and sporadic
medullary thyroid carcinoma

1996  Special Seminar, Institut Curie, Paris, France: Mapping of the Cowden
disease susceptibility gene: clue to BRCA3?

1996  Medical Genetics Seminar, Institut Necker, Hôpital des Enfants-Malades,
Paris, France: Mutations in the RET proto-oncogene in MEN 2 and
Hirschsprung disease

1996  Department of Endocrinology Seminar, King's College Hospital School of
Medicine, London, UK: RET proto-oncogene in MEN 2 and sporadic MTC

1996  Department of Endocrinology Seminar, St. Bartholomew's Hospital,
London, UK: Localisation of the gene for Cowden disease: another breast
cancer susceptibility gene?

1996  Special Seminar, Department of Medical Genetics, Queen's University,
Kingston, ON: Cowden syndrome

1997  Université Claude Bernard Lyon I, Lyon, France: External examiner, PhD
thesis committee (PhD Candidate: Isabelle Schuffenecker)

1997  Special Seminar, International Agency for Research on Cancer, Lyon,
France: Molecular genetics of Cowden syndrome

1997  Special Seminar, Cancer Institute of New Jersey, New Brunswick, NJ:
PTEN in Cowden syndrome

1997  31st Patterson Symposium: Li-Fraumeni syndrome, Manchester, UK: Two-
dimensional gene scanning for rapid p53 mutation detection

1997  IV International Thyroid and Neuroendocrine Cancer Workshop, Sicily,
Italy: Genotype-phenotype correlations in MEN 2 and genotype-prognosis
studies in sporadic medullary thyroid carcinoma

1998  Special Seminar, Fox Chase Cancer Center, Philadelphia: PTEN, encoding
a dual specificity phosphatase, in inherited hamartoma-tumor syndromes

1998  Endocrine Grand Rounds, Mt. Sinai Medical Center, NY: The RET proto-
oncogene in inherited and sporadic medullary thyroid carcinoma

1998  Special Seminar, Human Cancer Genetics Program, Comprehensive Cancer
Center, Ohio State University, Columbus, OH: The paradox of the RET
proto-oncogene: multiple endocrine neoplasia and Hirschsprung disease

1998  Special Seminar, Human Cancer Genetics Program, MD Anderson Cancer
Center, Houston, TX: PTEN in inherited hamartoma-tumour syndromes

1998  Invited Lecture, First International Lentigenosis Meeting, National Institutes
of Health, Bethesda, MD: PTEN, Cowden syndrome and Bannayan-
Ruvalcaba-Riley syndrome

1998  Invited Symposium Lecture, Fourth European Congress of Endocrinology,
Seville, Spain: RET and PTEN mutations in sporadic thyroid tumours

1998  Invited Lecture, ASCO Continuing Medical Education Course “Cancer
Genetics in Office Practice,” Princeton, NJ: Genetics of colorectal cancer

1998  Breast Cancer Research Centre, Vancouver, BC: PTEN and its role in
breast tumourigenesis in Cowden syndrome
1998 Invited Lecture, 54th Recent Progress in Hormone Research, Skamania Lodge, Stevenson, WA: PTEN, encoding a phosphatase, in hereditary and sporadic nonmedullary thyroid tumors
1998 Invited Lecture, International Congress on Hereditary Cancer Diseases, Düsseldorf, Germany: Cowden syndrome: update on genetic mechanisms and clinical features
1998 Grand Rounds, University of Michigan Cancer Center, Ann Arbor, MI: The yin and yang of inherited thyroid cancer
1998 Invited Lecture, American Psychological Association Conference on Behavioral Science and Genetics, Tyson’s Corner, VA: Genetic testing: from technology to treatment
1998 Karolinska Institute, Stockholm, Sweden: Faculty Opponent for PhD Thesis Defence (PhD Candidate: Filip Farnebo)
1999 Grand Rounds, NIDDK, NIH, Bethesda, MD: Genetic and epigenetic PTEN alterations in inherited and sporadic neoplasia
1999 Invited Lectures, NIH-sponsored Phakomatosis Revisited Workshop Rockville, MD: Hamartoses; Cowden syndrome and PTEN
1999 Invited Lecture, ASCO Train the Trainer Update: Bringing Cancer Genetics to Office Practice, New Orleans, LA: Molecular diagnosis of the inherited hamartoma tumor syndromes
1999 Medicine Grand Rounds, Rush Medical School, Chicago, IL: Molecular genetics in office practice: RET proto-oncogene mutations in multiple endocrine neoplasia type 2
1999 Molecular Medicine Seminar, University of Toronto, Canada: Genetics of PTEN in inherited and sporadic cancers
1999 Invited Symposium Lecture, American Gastroenterological Association, Orlando, FL: Feast or famine: RET proto-oncogene in intestinal ganglioneuromatosis and Hirschsprung disease
1999 Invited Plenary Lecture, Seventh International Workshop on Multiple Endocrine Neoplasia, Gubbio, Italy: MEN 2 and the practice of molecular oncology
1999 Invited Plenary Lecture, Seventh International Workshop on Multiple Endocrine Neoplasia, Gubbio, Italy: The role of PTEN in Cowden syndrome and multiple sporadic cancers

C. Short Report of Clinical Activities

Description of Clinical Practice: Clinical cancer genetics; medical oncology, especially inherited hamartoma tumor syndromes, and endocrine tumors in a teaching hospital setting.

Patient Load: 20% effort in the practice of clinical cancer genetics. Patients/families seen in cancer genetics clinic are usually complex and labor intensive.

Clinical Contributions: When we and other groups discovered that germline mutations in the RET proto-oncogene are associated with MEN 2, clinical diagnostic testing became available within 6 months of our publication. Since then, our work as well as others' work have borne out initial data, such that RET testing has now become the clinical standard of care in MEN 2 and all cases of medullary thyroid cancer. Mutation status is important in these entities because it alters clinical
management for the patient and his/her family. I have also worked with at least one CLIA-certified laboratory to ensure quality control and have worked with at least one third party insurer so that RET testing is covered 100%.
Bibliography

Original Reports:


58. Marsh DJ, Andrew SD, Learoyd DL, Pojer R, Eng C, Robinson BG. Deletion-insertion mutation encompassing RET codon 634 is associated with medullary thyroid carcinoma. *Hum Mutat* 1997; Mutations in Brief #12 Online.


122. Yeh JJ, Marsh DJ, Zedelius J, Dwight T, Delbridge L, Robinson BG, Eng C. Fine structure deletion analysis of 10q22-24 demonstrates novel regions of loss and suggests
that sporadic follicular thyroid adenomas and follicular thyroid carcinomas develop along distinct parallel neoplastic pathways. *Gene Chrom Cancer* (in press)

Reviews:


17. **Eng C.** From bench to bedside ... but when? *Genome Res* 1997; 7:669-72.


**Books and Other Monographs:**


Abstracts:


12. Ponder B, Mulligan L, **Eng C**, Edery P, Lyonnet S, Smith D, Tunncliffe A, Kwok J. The multiple endocrine neoplasia type 2 syndromes and Hirschsprung disease are due to different mutations in the receptor tyrosine kinase RET. *Fourth European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumors*, Netherlands, April, 1994.


17. Eng C, Toogood AA, Ponder BAJ, Shalet SM. A family with multiple endocrine neoplasia type 2B which does not have a mutation at codon 918 of exon 16 of the RET proto-oncogene. J Endocrinol 1995; 144S:P44.


34. Syngal S, Fox E, Eng C, Garber JE, Kolodner DR. Presence of more than one hMSH2 and hMLH1 mutation in four hereditary nonpolyposis colon cancer (HNPCC) kindreds. Gastroenterol 1997; 112:A664.


70. Yeh JJ, Lunetta KL, Dahia PLM, Eng C. Mitochondrial DNA (mtDNA) mutations in papillary thyroid carcinoma and differential mtDNA sequence variants in cases with malignant versus benign thyroid tumors. Am J Hum Genet 1999; 64S (in press)


Newsletters and Misc.:


2. Writer for Trends in Genetics Monitor, 1994