Commentary

Will the real Cowden syndrome please stand up: revised diagnostic criteria

Charis Eng

Clinical Cancer Genetics and Human Cancer Genetics Programs, Comprehensive Cancer Center, and Division of Human Genetics, Department of Internal Medicine, The Ohio State University, 420 W 12th Avenue (Suite 690 MRF), Columbus, OH 43210, USA; CRC Human Cancer Genetics Research Group, University of Cambridge, Cambridge, UK

Correspondence to:
Professor Eng,
eng-1@medctr.osu.edu

Cowden syndrome (CS, MIM 158350) is an autosomal dominant disorder with age related penetrance characterised by multiple hamartomas and a high risk of breast, thyroid, and perhaps other cancers. These hamartomas can arise in tissues derived from all three embryonic germ cell layers, in accordance with the prominent expression of the susceptibility gene throughout human embryonic and fetal development.[1] The cardinal features of CS include trichilemmomas, which are hamartomas of the infundibulum of the hair follicle, and mucocutaneous papillomatous papules, which occur in the great majority (>90%) of affected subjects.[2 3] Lesions in the breast or thyroid occur in at least two thirds of CS cases. The incidence of CS before gene identification was estimated to be 1 in a million in a population based Dutch clinical epidemiological study.[2 4] However, after gene identification, this figure was revised to 1 in 200 000,[5] which is almost certainly an underestimate. This is because CS has variable expression and often can have nothing but subtle skin signs, and so this condition is difficult to recognise and remains underdiagnosed.

Table 1 International Cowden Consortium operational criteria for the diagnosis of CS, Ver 1995

Pathognomonic criteria
Mucocutaneous lesions
Trichilemmomas, facial
Acral keratoses
Papillomatous lesions
Mucosal lesions
Major criteria
Breast carcinoma
Thyroid carcinoma, especially follicular thyroid carcinoma
Macrocephaly (eg, ≥95th centile)
Lhermitte-Duclos disease (LDD)
Minor criteria
Other thyroid lesions (eg, goitre)
Mental retardation (say, IQ ≤75)
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
GU tumours (eg, uterine fibroids) or malformation
Operational diagnosis in a person
(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) palmoplantar 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 person is diagnostic for Cowden syndrome
(1) The pathognomonic criterion/ia
(2) Any one major criterion with or without minor criteria
(3) Two minor criteria

Before 1996, little was known about the molecular aetiology of the inherited hamartoma syndromes, including CS. For purposes of localising the CS gene, the International Cowden Consortium proposed a set of operational diagnostic criteria to ascertain CS families and to assign affected status within families (table 1).[4 6] These criteria have been adopted by the US based National Comprehensive Cancer Network (NCCN) Genetics/High Risk Cancer Surveillance Panel, whose task is to present evidence based or expert consensus practice guidelines.[7]

The susceptibility gene for CS was mapped to 10q22-23 and identified a year later as *PTEN*.[4 8] PTEN is an almost ubiquitously expressed dual specificity phosphatase which acts as a tumour suppressor[9–11] by mediating cell cycle arrest or apoptosis or both, among other as yet unelucidated functions.[12–14] When CS families and cases are ascertained strictly by the Consortium criteria (table 1), the *PTEN* mutation frequency is approximately 80%.[8 15] However, when these criteria are not used, the mutation frequency ranges from 10-50%.[16–18] Bannayan-Riley-Ruvalcaba syndrome (BRR, MIM 153480), an autosomal dominant developmental disorder characterised by macrocephaly, developmental delay, lipomatosis, haemangiomatosis, and speckled penis, is allelic to CS,[19] with a mutation frequency of 50-60%.[20] The highest *PTEN* mutation frequencies (>92%) are consistently obtained in CS-BRR overlap families (Eng and Hampel, 2000, unpublished observations).[20] Recently, a Proteus syndrome-like subject was found to have a germline *PTEN* mutation and a germline mosaic *PTEN* mutation.[21] This Proteus-like patient presented at birth with marked hypertrophy of the right lower extremity in girth and length, pink verrucoid epidermoid naevi in whirls and plaques on the right side of his body, and macrocephaly. The hemihypertrophy progressed such that massive arteriovenous malformations involving the muscles and bones of the entire right lower extremity and pelvis were noted at the age of 6 years. This patient does not meet the diagnostic criteria for Proteus syndrome[22] nor BRR.[23] A de novo germline *PTEN* R335X was found in this case, and non-germline R130X was found in three different non-contiguous affected tissues from the hypertrophied lower extremity.[21] Whether

Table 2 International Cowden Consortium operational criteria for the diagnosis of CS, Ver 2000

Pathognomonic criteria
Mucocutaneous lesions
Trichilemmomas, facial
Acral keratoses
Papillomatous papules
Mucosal lesions
Major criteria
Breast carcinoma
Thyroid carcinoma (non-medullary), especially follicular thyroid carcinoma
Macrocephaly (megalencephaly) (say, ≥95th centile)
Lhermitte-Duclos disease (LDD)
Endometrial carcinoma
Minor criteria
Other thyroid lesions (eg, adenoma or multinodular goitre)
Mental retardation (say, IQ ≤75)
GI hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
GU tumours (eg, **renal cell carcinoma**, uterine fibroids) or malformation
Operational diagnosis in a person
(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) palmoplantar keratoses, 6 or more
(2) 2 major criteria but one must include macrocephaly or LDD
(3) 1 major and 3 minor criteria
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Operational diagnosis in a family where one person is diagnostic for Cowden syndrome
(1) The pathognomonic criterion/ia
(2) Any one major criterion with or without minor criteria
(3) Two minor criteria

Operational diagnostic criteria are reviewed and revised on a continuous basis as new clinical and genetic information becomes available.

other Proteus-like cases will have *PTEN* mutations is unknown and is the subject of continuing research. It has been proposed that these syndromes that are defined by germline *PTEN* mutations be collectively termed *PTEN* Hamartoma Tumour Syndrome or PHTS.[20]

In an effort to determine the full clinical spectrum involved in *PTEN* mutation and to confirm the robustness of the Consortium criteria, a study was performed to examine germline *PTEN* mutations in families and subjects ascertained by the minimal presence of breast cancer and any anatomical thyroid disorder in a single person or in a minimum of two first degree relatives in a family but who did not meet the Consortium criteria for the diagnosis of CS.[24] Of 64 CS-like cases ascertained, one was found to have a germline *PTEN* mutation. This family had bilateral breast cancer, follicular thyroid carcinoma, and endometrial adenocarcinoma. There were only four other families with endometrial cancer. These observations suggest that the Consortium criteria are robust and that the small but finite *PTEN* mutation frequency is important in clinical cancer genetic management. Further, it suggests that the presence of endometrial cancer may increase the likelihood of finding germline *PTEN* mutation, even in CS-like families. In another recent study, a nested cohort comprising 103 eligible women with multiple primary cancers within the 32 826 member Nurses' Health Study were examined for the occult presence of germline *PTEN* mutations.[25] Among 103 cases, five (5%) were found to have germline missense mutations, all of which have been shown to cause some loss of function. Of these five, two cases themselves had endometrial cancer. This study, therefore, suggests that occult germline mutations of *PTEN*, and by extrapolation CS, occur with a higher frequency than previously believed. Further, these data confirm the previous observations[24] that endometrial carcinoma might be an important component cancer of CS and, indeed, its presence in a case or family that is reminiscent of CS but does not meet Consortium criteria might actually help increase the prior probability of finding *PTEN* mutation. Taken together, these molecular based observations, together with previous clinical epidemiological studies,[2] were felt sufficient to revise the Consortium criteria for the diagnosis of CS to include endometrial carcinoma (table 2). These revised criteria will most likely be adopted for the next revision of the NCCN document. Although further long term and formal investigation of whether endometrial carcinoma and other tumours are true components of CS, for purposes of research ascertainment and for clinical practice, exponents of CS and the NCCN panel felt that it would be more conservative, and in the interest of the patient, to acknowledge endometrial carcinoma as a component cancer.

Anecdotal evidence suggests that renal cell carcinoma and malignant melanoma may be minor component neoplasias of CS, although the latter association is difficult to prove because melanoma is common in the general population as well. Nonetheless, they should be kept in mind, especially when considering surveillance in PHTS.

Surveillance recommendations are governed by the component tumours of CS, namely, breast carcinoma, non-medullary thyroid carcinoma, adenocarcinoma of the endometrium, renal cell carcinoma, and possibly melanoma. For males and females, annual comprehensive physical examinations paying particular attention to skin changes and the neck (thyroid) region should be instituted at the age of 18 years or five years younger than the youngest diagnosis of a component cancer in the family.[7] For females, annual clinical breast examination and training in breast self examination should begin around the age of 25 years; annual mammography should begin at 30 or five years younger than the earliest age of breast cancer diagnosis in the family.[7] For the next NCCN revised guidelines, the panel would probably also recommend annual surveillance of the endometrium, blind repel (suction) biopsies of the endometrium in the premenopausal years, perhaps beginning at the age of 35 or five years younger than the youngest age of endometrial cancer diagnosis in the family, as well as annual urine analysis for the presence of blood which may be performed together during the annual physical examination. Further, clinicians who look after such families should be mindful to note any other seemingly non-component neoplasia which might be over-represented in a given family.

Who should undergo CS surveillance? Any person known to have a germline *PTEN* mutation (that is, PHTS) should undergo surveillance. Among classical CS and BRR probands, preliminary data suggest that the presence of a *PTEN* mutation is associated with the

development of breast cancer in any given family.[15 20] Until further data become available, any subject who carries the clinical diagnosis of CS should also undergo surveillance. What is less clear is whether *PTEN* mutation negative BRR should undergo cancer surveillance.

I am deeply grateful to all the patients and families with CS, BRR, and CS-like from around the world who have participated in our studies. I would also like to thank members of my laboratory, numerous collaborators and colleagues, especially Mark Greene and Monica Peacocke, and all the genetic counsellors, especially Heather Hampel and Kathy Schneider, who have contributed in one way or another towards the formulation of these revised criteria. My research activities are funded by the National Institutes of Health, Bethesda, MD, USA, the American Cancer Society, the US Army Breast Cancer Research Program, the Susan G Komen Breast Cancer Research Foundation, and the Mary Kay Ash Charitable Foundation.

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