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Familial Colorectal Cancer Type X: the other half of Hereditary Non-Polyposis Colon Cancer Syndrome

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Synopsis

Establishing the Amsterdam Criteria, based on pedigrees, was essential to defining HNPCC syndrome in such a way that identification of the underlying genetic etiology could be accomplished. It is now known that about half of families that fulfill the original Amsterdam Criteria have a hereditary DNA mismatch repair gene mutation. These families may be said to have Lynch Syndrome. The other half of HNPCC families have no evidence of DNA mismatch repair deficiency and studies now show that these families are different from Lynch Syndrome families. Familial Colorectal Cancer Type X is the name used to refer to the “other half of HNPCC”.

Keywords

cancer; colorectal; familial; hereditary; non-polyposis; HNPCC

As the story goes, the seamstress of Dr. A. Warthin predicted that she would die of either cancer of the stomach or female organs, as that is what happened in to her family members, and indeed, this proved to be true. Dr. Warthin, a pathologist at the University of Michigan began a systematic study of this family, which he called “Family G”, confirming the cancer diagnoses with histologic diagnoses and he published on Family G in 1913 (Warthin’s contribution reviewed by Merg) [1, 2]. He subsequently identified other families with similar predisposition to cancer and continued to study, follow, and report on these families into the 1920s. After Warthin, there was general silence in the literature on this subject until a young general internist, Dr. Henry Lynch, began to draw attention once again to families like Family G. He observed that a subset of families with colorectal cancer appeared to manifest a highly penetrant, autosomal dominant predisposition to colorectal cancer and endometrial cancer. The ages at diagnosis were much younger than was characteristic for those tumors, and the colorectal cancers were located disproportionately in the right colon [3] He struggled to achieve recognition of this syndrome, as environmental etiologies of cancer were much more accepted than the possibility that cancer could be hereditary. However, other practioners gradually began to identify new families that conformed to the Warthin-Lynch observations and the significance of the family history began to emerge in

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cancer studies. There were few non neoplastic or preneoplastic features to distinguish Lynch's families from sporadic cancer cases and this clinical entity was given the descriptive name HNPCC, though there was no formal definition how to recognize or diagnosis this syndrome. Finally, in 1991, following a meeting in Amsterdam, the International Collaborative Group on Hereditary Non-Polyposis Colon Cancer published the Amsterdam I criteria (AC-I) for defining HNPCC [4]. The AC-I are fulfilled if all four of the following conditions are met: (1) three cases of colorectal cancer (CRC) in which two of the affected individuals are 1st-degree relatives of the third; (2) CRCs occurring in 2 generations; (3) one CRC diagnosed before the age of 50 years; and (4) familial adenomatous polyposis not diagnosed in the family. Creating a standard definition for HNPCC lead rather promptly to identification of germline mutations in DNA mismatch repair genes as a cause of Warthin-Lynch syndrome which came to be called HNPCC by most scientists. Further studies confirmed the dramatically increased risks for cancers of the colorectum and endometrium, and also found significantly increased risks for carcinomas of the stomach, small intestine, hepatobiliary tract, kidney, ureter, and ovary. Based upon current understanding of the cumulative risks for specific cancers, expert guidelines were provided that stressed cancer surveillance that was to be initiated at very young ages and to be conducted with greater frequency than advised in the general population [5].

Following the discovery of mutations in the DNA mismatch repair genes in families with typical Warthin-Lynch HNPCC, the term "HNPCC" began to be used ambiguously in the medical literature. Some publications defined HNPCC by kindred fulfillment of the Amsterdam criteria (either the original criteria, or the revised criteria [4, 6]). Some articles stressed that the Amsterdam Criteria were designed for research purposes and were overly restrictive for clinical use, but they were used clinically anyhow. Over time, the term HNPCC sometimes came to imply the presence of a germline mutation in a DNA mismatch repair gene, especially in laboratory research publications. If all families that fulfilled the Amsterdam Criteria actually had germline mutations in DNA mismatch repair genes, this would be nothing more than a semantic problem. However, there was clear evidence that fulfillment of AC-I was not equivalent to having a hereditary DNA mismatch repair gene mutation [7, 8] (and others). In reporting on 184 probands from 92 Amsterdam Criteria-positive families, mutations in *MLH1* or *MSH2* were found in only 45% of those meeting the criteria [8]. Indeed, despite the discovery of *MSH6*, *PMS2*, methods to test for large deletions or and use of tumor microsatellite instability testing to help triage cases for germline testing, most studies suggest only 50–60% of families that fulfill the original Amsterdam Criteria have a defect in DNA mismatch repair. Note that the Amsterdam II criteria, which expands definition to some of the extracolonic tumors, has a greater sensitivity for underlying hereditary DNA mismatch repair defect [8] (and others).

For those half of "HNPCC" families that fulfilled AC-I but did not have DNA mismatch repair gene defects, there was little data on cancer risks or phenotype and not even a name to distinguish this group from those with the germline defects-- they were all included, by pedigree definition, as HNPCC. But should clinicians counsel that such families needed the rigorous cancer surveillance and endometrial cancer recommendations driven by the risks associated with hereditary DNA mismatch repair gene mutations? Or might both the magnitude of risks and tumor spectrum be different?

In the largest study to date, the relative risks for cancers were compared in 161 Amsterdam I Criteria families from the NIH Colon Cancer Family Registry, comparing those families with DNA mismatch repair defects and those families without DNA mismatch repair defects [9]. Microsatellite instability in the proband tumor was used to assign mismatch repair status. Ninety families had DNA mismatch repair deficiency and 71 did not. For purposes of analysis, the Amsterdam-defining "triad" of three affected individuals, which always

included the proband, was not included in assessment of cancer risks. The remaining 3,422 relatives were either first- or second- degree relatives of a triad member. The incidence of cancer in these relatives was calculated as the ratio of observed to expected cases to the number of at-risk person-years (standardized incidence ratio; SIR). In the families with DNA mismatch repair-deficient tumors, the risk for cancers was statistically significantly elevated for colorectal, endometrial, gastric, small intestine, and kidney/ureter cancers as expected for Lynch syndrome, affirming that the methodology was adequate to detect appropriate information. However, in the 71 families without DNA mismatch repair deficiency, only a two-fold increased risk for colorectal cancer was detected (SIR 2.3; 95% CI 1.7–3.0), and no other cancer site reached statistical significance for increased risk. An age difference was also apparent: the average age at diagnosis of CRC was older (61 years) in the families with the tumors with normal DNA mismatch repair compared with families with DNA mismatch repair deficiency (49 years). Based upon these data, we concluded that families who fulfill the AC-I should not be managed as if they have hereditary DNA mismatch repair defect because the cancer risks are lower and appear to be restricted to colorectal cancers. Use of the term “Lynch Syndrome” was embraced to describe families with hereditary DNA mismatch repair defect and the term “Familial Colorectal Cancer Type X” was coined to refer to the other HNPCC-like clusters in which no DNA mismatch repair defect could be identified. The word “hereditary” was not included as familial clustering does not prove inheritance whereas the term hereditary may imply a Mendelian single-gene predisposition disorder, which has not been proven, nor strongly suspected. The choice of “Type X” was chosen as “X” is used as the unknown that needs to be solved in algebraic equations. A call has been made for retirement of the term, HNPCC, as it perpetuates the historical ambiguity of meaning [10].

The study cited above was by no means the first to try to tease apart molecular subsets of high risk families. Table 1 summarizes related studies.

An early consideration in Amsterdam Criteria-fulfilling families in which no MMR gene mutation could be found was whether the gene mutation was being missed or whether a hereditary MMR gene mutation created more subtle disturbances than could be detected with the usual assays for tumor microsatellite instability or immunohistochemistry. Renkonen et al [11] tested for allelic messenger RNA expression of *MLH1*, *MSH2* and *MSH6* by single nucleotide primer extension (SNuPE) in 26 pedigree-defined HNPCC families in which no MMR gene mutation had been detected. They found evidence for undetected germline mutation in an MMR gene in 9 of 11 families that manifest loss of expression of an MMR gene by tumor immunohistochemistry or microsatellite instability but in none of 15 families with microsatellite-stable (MSS) tumors and normal IHC expression of MMR genes. Specifically, they found evidence for undetected germline MMR mutations in their families with abnormal MMR gene function or expression in the form of unbalanced mRNA expression of *MLH1* in two of 11 families and by haplotype analysis in the others. However, in the MSS Amsterdam Criteria-fulfilling families, there was no evidence of hypomorphic alleles or undetected mutations in *MLH1*, *MSH2*, or *MSH6*. Schieman et al [12] also did extensive testing of 25 tumors from 19 Amsterdam-criteria positive cases and 6 Bethesda-guideline cases with reported MSS tumors. They were able to reclassify two (8%) as MSI-high, again suggesting that a missed diagnosis of Lynch Syndrome is not a major etiology for the Type X families.

To explore whether the tumors of Type X cases were similar to or different from those found in Lynch Syndrome or in sporadic CRC, Abdel-Rahman et al [13] analyzed the molecular features of the tumors in the pedigree-defined HNPCC-group from Finland in which no germline mutations were found or suspected. In comparing 31 tumors from MMR gene-positive families with 18 tumors from gene-negative families, it was concluded that the

MMR-gene negative group exhibited a novel molecular pattern characterized by a paucity of changes in the common pathways to colorectal carcinogenesis, distinguishing this group from both the Lynch syndrome cases as well as from sporadic colorectal cancer. This study supported the idea of novel predisposition genes and pathways for the Type X families (summarized in Table 2).

In contrast, a later study by Sanchez-de-Abajo et al [14] studied 28 tumors from 17 families in Spain that met Amsterdam I or II criteria but in which there was no evidence of MMR defects. *RAS*, *BRAF*, and *APC* somatic mutations were analyzed and expression of methylguanine methyltransferase (*MGMT*) and beta-catenin was assessed and these alterations were correlated with clinical data. This study also supported the concept that Type X families have distinctive molecular profiles. They reported *KRAS* mutations in 36%, which was similar to reported rates in Lynch Syndrome and in sporadic MSS CRCs. Thus the lower rate of *KRAS* reported by Abdel-Rahman et al [13] was not confirmed. However, they found the *KRAS* mutations were disproportionately in codon 12 (83%) compared to equal representation of *KRAS* mutations between codons 12 and 13 in Lynch Syndrome. The *KRAS* finding was more similar to sporadic CRCs. No association was reported between *KRAS* mutation and gender, tumor site or stage, but there was a strong association with older age at diagnosis. *BRAF* mutation, found in 3.6%, was not statistically different from Lynch Syndrome or sporadic CRCs. Thus the alteration in the RAS/RAF signaling pathway appeared quite similar between the Type X families and the sporadic MSS cancers leading the authors to suggest that some Type X families are classified as such due to chance aggregation of sporadic cases. On the other hand, the majority of the Type X CRCs had active WNT signaling due either to *APC* or *CTNNB1* mutations. The rate of *APC* mutation was low, 18%, compared with sporadic-MSS-CRCs, (34–70%) and similar to Lynch syndrome (21–27%), and, unexpectedly, small deletions/insertions in repetitive sequences accounted for 70% of mutations, mimicking the profile found in Lynch syndrome. Although the data was not entirely consistent with that reported by Abdel-Rahman et al [13], this group also found sufficient differences between the Type X group compared with sporadic CRCs and Lynch Syndrome CRCs to be considered distinctive and to warrant additional study.

Several groups have contributed to the clinical understanding of FCCTX. In a study of 41 German families, an older age at CRC diagnosis in FCCTX compared to Lynch Syndrome was noted (55 vs 41 years) and two thirds of the tumors were left-sided, the inverse of CRC in Lynch Syndrome. Their Lynch Syndrome group had more synchronous and metachronous CRCs, but the FCCTX group had greater adenoma/carcinoma ratio and a tendency toward more adenomas, suggesting a slower progression of adenomas to carcinomas [15]. A similar finding was reported based upon 97 families with dominant CRC family history in the United Kingdom: individuals with Lynch Syndrome and FCCTX had equal likelihood of having high risk adenomas but only those with Lynch Syndrome developed CRC [16]. Among 64 Spanish families that met Amsterdam Criteria, 40% had normal DNA mismatch repair in tumor (consistent with other studies) and an older age at CRC diagnosis in the FCCTX compared to Lynch Syndrome (53 vs 41 years); the FCCTX cases were less likely to be in the right colon, have mucinous tumors, and the families had fewer multiple primary tumors [17]. Llor et al [18] studied 100 individuals from 25 Spanish families meeting Amsterdam criteria, 40% of whom had normal DNA mismatch repair. Compared with families with known DNA mismatch repair defects, the mean age at diagnosis of CRC in relatives was older (60 vs 54 years), 89% of tumors were left sided, none showed tumor infiltrating lymphocytes (half of the Lynch Syndrome CRC showed this) [18]. Table 3 compares and contrasts Lynch Syndrome with FCCTX, based upon the reports from these multiple sources.

Familial Colorectal Cancer Type X (FCCTX) is undoubtedly a heterogeneous grouping. It likely includes some families that have a random aggregation of a common tumor; some families may be attributable to shared lifestyle factors and/or polygenic predisposition; and some families likely have a yet-to-be-defined syndrome or an undiagnosed single gene disorders, such as *MYH*-associated polyposis [19] or the MSI-variable families [20]. In a population-based study of 1,042 CRC probands with verified family histories, Aaltonen et al [21] explored how much of familial risk is attributable to Lynch Syndrome or other known genetic syndrome. When known syndromes were excluded from the analysis, 32% of familial risk remains unaccounted for by the known loci. Genetic modeling of the data did not suggest a better explanation than a simple polygenic model. Studies are now beginning to chip away at the genetic causes of FCCTX.

FCCTX is a diagnosis of exclusion. Care must be exercised in making this diagnosis. Classification depends heavily upon tumor microsatellite instability results and other laboratory results. One must consider the possibility of a phenocopy within a Lynch Syndrome family (i.e., a sporadic MSS tumor that arose by chance in a family that actually does have Lynch Syndrome); one must consider that not all tumors with germline *MSH6* mutations are MSI-high; one must consider laboratory factors such as the adequacy of the percentage of tumor cells in the MSI-assay and the small but real chance of a falsely normal immunohistochemistry result if this test is done without MSI testing. In general the age at diagnosis in the FCCTX families is older (see below) than in Lynch Syndrome families and in light of this consistent observation, families with young average age of onset of colorectal tumors or families manifesting other classical Lynch Syndrome tumors such as endometrial cancer should probably not be categorized as having FCCTX. Cancer screening recommendations have been suggested for FCCTX, such as offering CRC screening initiated 5 to 10 years prior to the age of earliest colorectal cancer diagnosis in these families, with frequency determined by initial findings but no less often than every 5 years. Aggressive endometrial cancer screening is not supported by current data [9, 16, 22]. As these guidelines are considerably different and less aggressive than those advised for families with Lynch Syndrome, it is essential to not miscategorize FCCTX families and to continue to reconsider the possibility of a single gene syndrome, as new disorders are described.

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Table 1

Overview of studies comparing Amsterdam Criteria families with DNA mismatch repair deficiency (Lynch Syndrome) and with normal DNA mismatch repair (Familial Colorectal Cancer Type X).

	Lynch families	Type X families	Comparison between the Lynch and Type X families
Bisgaard [7]	27	12 plus 46 other HNPCC-like	Mutation-negative group less likely to have more than one CRC, first cancer more likely to be rectal, less likely to have HNPCC-associated extracolonic tumors, and mean age at diagnosis of first cancer 6 years older.
Renkonen [11]	11	15b	No evidence of MMR gene mutations being missed in Type X group, using RNA expression assay
Schiemann et al [12]	NA	19	Type X tumors more likely to be in distal colorectum; 9 years older at diagnosis than MSI-H families
Valle [17]	26	38	Type X families 12 years older at diagnosis and CRC more likely to be distal, not mucinous, and probands less likely to have multiple primary tumors
Lindor [9]	90	71	Type X had older age and lower risk of diagnosis of CRC; no increased risk for non CRC tumors
Mueller-Koch et al [15]	25	16	Type X families 11 years older at diagnosis of CRC; only 14% tumors were proximal; fewer synchronous, metachronous, and extracolonic tumors; higher colorectal adenoma to carcinoma ratio suggesting slower progression from precancer to cancer.
Dove-Edwin [16]	26	45a	Groups equally likely to develop high risk adenomas during follow-up but interval cancers arose only in the Lynch Group. Concluded that surveillance interval can be lengthened in Type X
Llor [18]	10	15c	Type X had more left sided tumors without tumor-infiltrating lymphocytes; 6 years older at diagnosis; fewer family members with CRC or endometrial cancer,

^aWaived the one-person under 50 at diagnosis criteria so not defined as FCCTX in exactly the same way as in Lindor et al [9]

^bThese are HNPCC and HNPCC-like families - proportion of each is unclear

^cUsed both Amsterdam Criteria-I and II

NA Not applicable as not described in the paper.

Table 2

Adapted from Abdel-Rahman et al [13]

	Type X N=18 tumors	Lynch N=31 tumors	Sporadic from literature	P-value for Type X vs Lynch	P-value for Type X vs Sporadic
Nuclear beta-catenin	39%	81%	95%	0.005	0.000005
<i>CTNNB1</i> mutations	0%	29%	6%	0.007	NS
<i>CDX2</i> alteration: decreased protein	11%	6%	16%	NS	NS
<i>KRAS</i> exon 2 mutations	17%	26%	30%	NS	NS
<i>BRAF</i> V600E	4%	0%	3%	NS	NS
p53 protein stabilization	44%	13%	52%	0.04	NS
<i>TP53</i> mutation	26%	13%	52%	NS	0.01
Chromosomal instability by CGH	44%	Not done	79%		0.00006

NS=not significant; CGH= comparative genomic hybridization

Table 3

Contrasting two types of families that fulfill the pedigree Amsterdam-I Criteria (adapted from Familial Colorectal Cancer Type X In: Genetics of Colorectal Cancer, Chapter 8.2. JD Potter and NMLindor, Eds. Springer, Publishers. In press, 2008).

	Lynch Syndrome	Familial Colorectal Cancer Type X
Colorectal		
Cancer risk	very high	modestly increased
Age of onset	~ 45 years average	50s–60s
Usual location	proximal colon	distal colon
Polyps	Few	More
Malignant transformation	Rapid	Less rapid
Other cancers		
Endometrial risk	Very high risk	Risk not significantly increased
Other cancer sites	Many others	None known
Germline MMR genes	Mutations found	No mutations found
CRC tumor testing	Microsatellite instability	No microsatellite instability (by definition)
CRC Tumor staining	Loss of MMR protein expression	Normal expression

CRC = colorectal cancer

MMR = mismatch repair