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ORIGINAL ARTICLE

Familial atypical multiple mole melanoma (FAMMM) syndrome: history, genetics, and heterogeneity

Henry T. Lynch[1] · **Trudy G. Shaw**[1]

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Abstract Approximately 5–10 % of cutaneous melanoma occurs in kindreds with a hereditary predisposition. Mutations in the *CDKN2A* gene are found to occur in approximately 20–40 % of these kindreds. The first historical mention of what is now called the familial atypical multiple mole melanoma syndrome appears to be from 1820, with more reports throughout the 1950s, 1960s, and later years. In 1991, Lynch and Fusaro described an association between familial multiple mole melanoma and pancreatic cancer and work continues to elucidate the syndrome's genotypic and phenotypic heterogeneity. Individuals at risk for familial melanoma need periodic screenings. Unfortunately, adequate screening for pancreatic cancer does not currently exist, but pancreatic cancer's prominence in the hereditary setting will hopefully act as a stimulus for development of novel screening measures.

Keywords Familial atypical multiple mole melanoma syndrome · Hereditary melanoma · *CDKN2A* · Pancreatic cancer · Skin cancer

Introduction

The estimated number of cases of melanoma of the skin diagnosed in the United States in 2015 was 73,870, with the estimated number of deaths being 9940 [1]. Approximately 5–10 % of cutaneous melanomas occur in families with hereditary melanoma predisposition [2], suggesting that 3690–7390 cases of cutaneous melanoma in the US annually can be attributed to hereditary predisposition. Factors that can increase risk ten-fold include atypical moles, more than 100 typical moles, or family history of two first-degree relatives with melanoma. In general, familial melanoma cases have an earlier age at diagnosis than other melanoma cases (approximately 34 years compared with 54 years). In individuals with familial melanoma, cancer risk is 50–90 % [3].

Approximately 20–40 % of kindreds with familial melanoma worldwide have germline mutations in the *CDKN2A* gene, located on chromosome 9p21 [2]. Some *CDKN2A* mutations have been found to be associated with increased risk of other malignancies, most notably pancreatic carcinoma [2, 4]. Germline mutations in another gene, *CDK4*, are seen in only about 1 % of melanoma-prone families [3].

Historical perspective of the FAMMM

In a publication in 1820, Norris [5] gave perhaps the first historical hereditary example of the familial atypical multiple mole melanoma (FAMMM) syndrome, which he referred to as a "fungoid disease." It was evidenced initially in a 59-year-old male who noted that a tumor began to arise from a mole that had a brownish hue. The tumor was excised but again began to grow, becoming a prominent scirrhous-looking tumor, and minute tubercles surrounded the tumor. There were at least 40 of these lesions and they were of various sizes. The glands in the groin were swollen and slightly tender. Lancinating pains occasionally affected the diseased parts and an early symptom was an excruciating pain complained of near the right kidney. Nausea and loss of appetite allegedly appeared

✉ Henry T. Lynch
htlynch@creighton.edu

[1] Department of Preventive Medicine, Creighton University, 2500 California Plaza, Omaha, NE 68178, USA

accompanied by restlessness and excessive depression of spirits. "…The whole body seemed to participate in this disease of structure, and to preclude all idea of relief from any surgical operation, and to leave no resource beyond palliative treatment…" After death, it was found that the lesion had disseminated throughout the peritoneum and most internal organs including the heart and lungs.

Of interest, the patient's father had died of a similar disease and therein his surgeon informed Dr. Norris that a number of small tumors had appeared between the shoulders which were severely cauterized, with death following soon thereafter. The patient and his father, as well as the patient's brothers and children, had many moles on various parts of their bodies. The youngest son had one of these exactly in the same place where his father's disease first manifested itself. Norris stated that "…These facts, together with a case that has come under my notice, rather similar, would incline me to believe that this disease is hereditary".

In 1952, Cawley [6] described cutaneous malignant melanoma in a father and two of his three children and suggested a hereditary basis for the incident. Other reports of familial occurrences followed, including Anderson et al. [7] who described 22 such families in 1967; in one of these families, 15 individuals developed the cancer.

In 1968, Lynch and Krush [8] reported four families with multiple malignant melanomas, including one family which was subsequently described in more detail [9] in which the proband presented with his fifth histologically verified malignant melanoma at age 26. The proband's daughter began developing brown moles at the age of 2; at 9 years of age, a particularly large lesion was excised and histology findings were consonant with a FAMMM mole, being a compound nevus with moderate dysplasia. Other family members with reported cutaneous malignant melanoma (CMM) included the proband's mother, maternal aunt, maternal grandfather, and that grandfather's sister and her daughter. Also in 1968, Lynch et al. [10] described two families with intraocular malignant melanoma in multiple members.

In the early 1980s [11], segregation analysis gave statistical support to FAMMM as an autosomal dominantly inherited syndrome with reduced penetrance. Also during this time, Lynch et al. [12, 13] noted phenotypic variation in the FAMMM syndrome, involving cancers other than malignant melanoma. This led to the identification by Lynch and Fusaro [4] in 1991 of an association between the FAMMM syndrome and pancreatic cancer (PC). In the mid-1990s, an association was found between both malignant melanoma [14, 15] and PC [16] and mutations in the *p16* (later called *CDKN2A*—cyclin-dependent kinase inhibitor 2A) gene. In 2000, Vasen et al. [17] determined that FAMMM kindreds with a specific mutation, which they termed *p16-Leiden*, were especially prone to PC. Work has continued in elucidating the phenotypic and genotypic heterogeneity of the FAMMM syndrome [18].

Potjer et al. [19]. recently noted that the *p16-Leiden* founder mutation in the *CDKN2A* gene is the most frequent etiology for the FAMMM syndrome in the Netherlands. Manifesting this mutation increases the risk of developing cutaneous malignant melanoma in addition to PC. Nevertheless, there is a striking interfamilial variability in the occurrence of PC among *p16-Leiden* families. Potjer et al. aimed to determine whether prior genetic risk identification factors for PC may modify the risk of PC in *p16-Leiden* germline mutation carriers. These authors studied 7 PC-associated SNPs which were selected from the literature and were genotyped in a cohort of 185 *p16-Leiden* germline mutation carriers from 88 families which included 50 cases with a median age of 55 years with PC and 135 controls with a median age of 64 years in the absence of PC. Their findings showed "…Allelic odds ratios per SNP were calculated; Results: No significant association with pancreatic cancer was found for any of the seven SNPs; Conclusions: Since genetic modifiers for developing melanoma have already been identified in *CDKN2A* mutation carriers, this study does not exclude that genetic modifiers do not play a role in the individual pancreatic cancer risk in this cohort of *p16-Leiden* germline mutation carriers. The search for these modifiers should therefore continue, because they can potentially facilitate more targeted pancreatic surveillance programs".

Typical FAMMM-PC pedigrees

Figure 1a, b show typical FAMMM families with involvement of CMM and PC. The family in Fig. 1a has three cases of PC with individual III-2, who carries the *CDKN2A* mutation, being affected by both CMM and PC. Other family members with PC were this individual's father (II-2) and paternal aunt (II-1). Individual III-2's sister (III-3) has shown CMM as has a cousin (III-1) who tested positive for *CDKN2A* mutation. Three of individual III-2's children (IV-4, IV-5, IV-6), all of whom tested positive for the family's *CDKN2A* mutation, have manifested CMM and the fourth (IV-7), who has not been tested, has exhibited atypical nevi. One grandchild of III-2 (V-1), positive for the *CDKN2A* mutation, has manifested CMM and another grandchild (V-3), who has not been tested, has been identified with atypical nevi. Of interest, two of individual III-1's children (IV-1, IV-3) tested negative for the *CDKN2A* mutation and have been found to have normal nevi.

The proband in Fig. 1b (III-8) manifested CMM at age 39 and died of PC at age 45; she was a *CDKN2A* mutation carrier, as are her two brothers (III-9, III-11). One of the brothers (III-9) has been affected by CMM and the other (III-11) has manifested histologically dysplastic nevi. Two

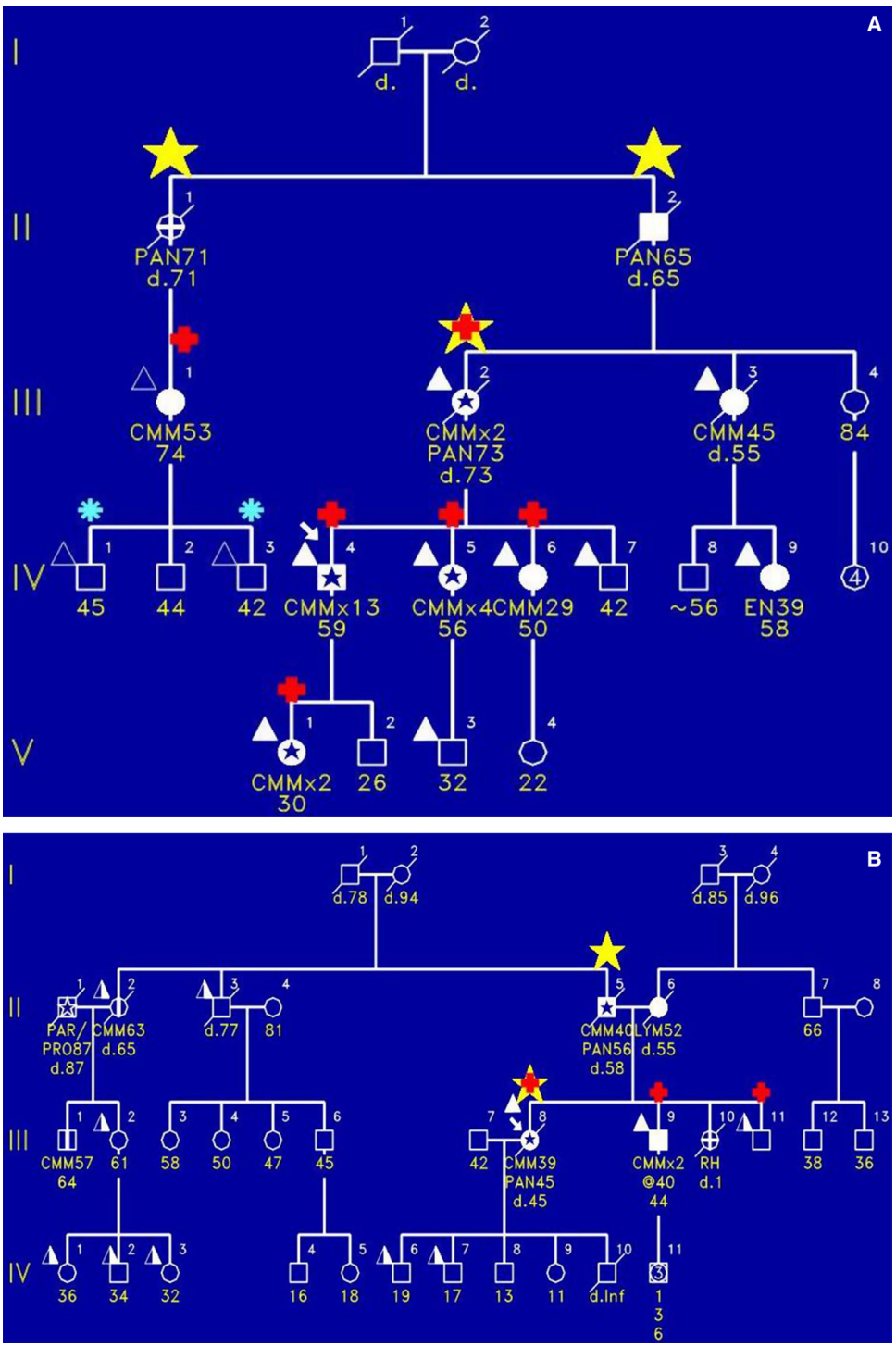

Fig. 1 Pedigrees of FAMMM syndrome families. Pancreatic cancer. Atypical nevi. Histologically atypical nevi. Normal nevi. Tested positive for *CDKN2A* mutation. Tested negative for *CDKN2A* mutation. Individuals with multiple cancers. *CMM* cutaneous malignant melanoma, *PAN* pancreatic cancer, *PAR* parotid cancer, *PRO* prostate cancer, *RH* rhabdomyosarcoma, *EN* endometrial cancer, *d.* died [age]. Pedigrees republished from Lynch et al. [27]. Copyright by the authors

of the proband's children, who have not been tested for the mutation (IV-6, IV-7), have shown histologically dysplastic nevi. The proband's father (II-5) had both CMM and PC and one of his sisters (II-2) as well as that sister's daughter (III-2) had CMM. A number of other members of the paternal linage have been identified with histologically dysplastic nevi (II-3, III-2, IV-1, IV-2, IV-3).

Cancer control in FAMMM-PC

The risk for developing melanoma in patients with dysplastic nevi has usually been found to be associated with the total clinically observable nevi count and an individual's history of melanoma. Histologic criteria can reliably distinguish atypical melanocytic nevi (AMN)-severe forms from AMN-mild and AMN-moderately dysplastic or atypical forms [20]. A more full interpretation of the potential risk for melanoma and the decision to excise an atypical nevus will be greatly influenced by medical history.

Familial melanoma should be considered in cases with two first-degree relatives with melanoma; a single individual with multiple primary melanomas even in the absence of a family history; a family history of melanoma, pancreatic cancer, and astrocytoma; and an individual with 10–100 dysplastic nevi [3].

Patients who are at risk for melanoma, especially members of FAMMM families, will need surveillance at periodic intervals for melanoma. The frequency of the surveillance will depend upon the degree of risk (e.g., patient with many atypical nevi may need biannual examination). Patients at risk for CMM should do complete self-examination every 3 months, looking for any perceived changes in color, size, and shape of their nevi. In such individuals, any suspicious lesions, including changes in moles/freckles and non-healing sores, should be promptly excised [3]. Digital dermoscopy has been found to be a useful part of surveillance for FAMMM patients [21].

Skin self-examination has the potential to reduce mortality from melanoma, possibly by as much as 63 % [22]. The use of dermoscopy in self-examination is being explored [23, 24], with utilization of mobile "smartphones" a promising approach [24–26].

The cure for PC is surgically dependent. Unfortunately, in the case of PC effective screening is lacking. However, PC's prominence in the hereditary setting will hopefully act as a stimulus for development of novel screening measures.

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