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Delineation of a new syndrome: clustering of pyloric stenosis, endometriosis, and breast cancer in two families

EDITOR—Familial tendencies have previously been observed for congenital pyloric stenosis, endometriosis, and breast cancer. These conditions have never been considered to have shared aetiological origins and consequently no previous attempts have been made to investigate an association. For example, when obtaining family history information for a child with pyloric stenosis, one would not routinely request a description of adult onset conditions such as endometriosis or breast cancer. Two families sharing an unusual clustering of these three conditions (pyloric stenosis, endometriosis, and breast cancer) were ascertained at the familial cancer clinics of the Women's College and Princess Margaret Hospitals in Toronto.

Family 1 (fig 1) contains four confirmed cases of breast cancer (below age 60), seven cases of endometriosis, five cases of congenital pyloric stenosis, nine cases of polycystic ovaries, and four cases of non-insulin dependent diabetes. In a second unrelated family, a woman previously diagnosed with premenopausal breast cancer, endometriosis, and pyloric stenosis reported one other case of congenital pyloric stenosis and four other cases of endometriosis in her family (fig 1). It is the similar and unusual presentation in these two families which suggests that the clustering of pyloric stenosis, endometriosis, and breast cancer may not be the result of chance.

A family history of breast cancer is known to be the most significant risk factor for developing the disease. Approximately 5-10% of all cases are hereditary and accounted for by mutations in cancer susceptibility genes *BRCA1* and *BRCA2*.[1 2] Family 1 met our criteria for *BRCA1* and *BRCA2* testing, with four known cases of breast cancer diagnosed below the age of 60. Mutation analysis by direct sequencing of the coding regions of *BRCA1* and *BRCA2* as well as 1700 adjacent non-coding intronic base pairs was performed by Myriad Genetic Laboratories (http://www.myriad.com). No *BRCA* mutation was identified for family 1. Family 2 was not tested for *BRCA1* or *BRCA2* mutations.

The aetiology of endometriosis remains uncertain, although familial trends have been described.[3] Four studies found that there is an increased risk among first degree relatives.[4–7] A small twin study found 6/8 monozygotic and 0/2 dizygotic twin pairs had endometriosis.[7] In family 2, five women in three generations had endometriosis and in family 1 seven women in three generations were given the diagnosis. The pattern of inheritance is consistent with sex limited, autosomal dominant inheritance.

A multifactorial genetic contribution for pyloric stenosis has been well established, although its pathological basis remains unknown. Twin studies have shown that there is a 25-40% concordance rate in monozygotic twins.[8 9] Based on pooled data from several family studies and assuming a population prevalence of 0.3%, a relative risk for first degree relatives compared to the general population was 18[10]; however, population based studies (unselected patients) have not been done. Pyloric stenosis has recently been linked to the locus of the neuronal nitric oxide synthase (*NOS1*) gene, based on 27 families.[11] The *NOS1* locus was also examined for other multifactorial conditions such as asthma (candidate gene)[13 14] and multiple sclerosis (no association).[15] Family 1 has five documented cases of surgically corrected pyloric stenosis in three males and two females. Family 2 has a parent and child with PS, both female.

In addition to endometriosis, family 1 contains nine women with polycystic ovary syndrome (PCOS), including one woman with non-insulin dependent diabetes mellitus (NIDDM). PCOS and NIDDM have been shown to have a shared aetiology.[12] Women with PCOS have a unique disorder of insulin action and are at increased risk of developing NIDDM, which occurs substantially younger (in the third to fourth decades) than it does in the general population.

Breast cancer, endometriosis, and pyloric stenosis in families 1 and 2 may be explained by separate genetic predispositions; however, the possibility that there is a common genetic basis exists. It is the complex interplay between environmental, hormonal, and genetic factors which poses a challenge to understanding the aetiology of

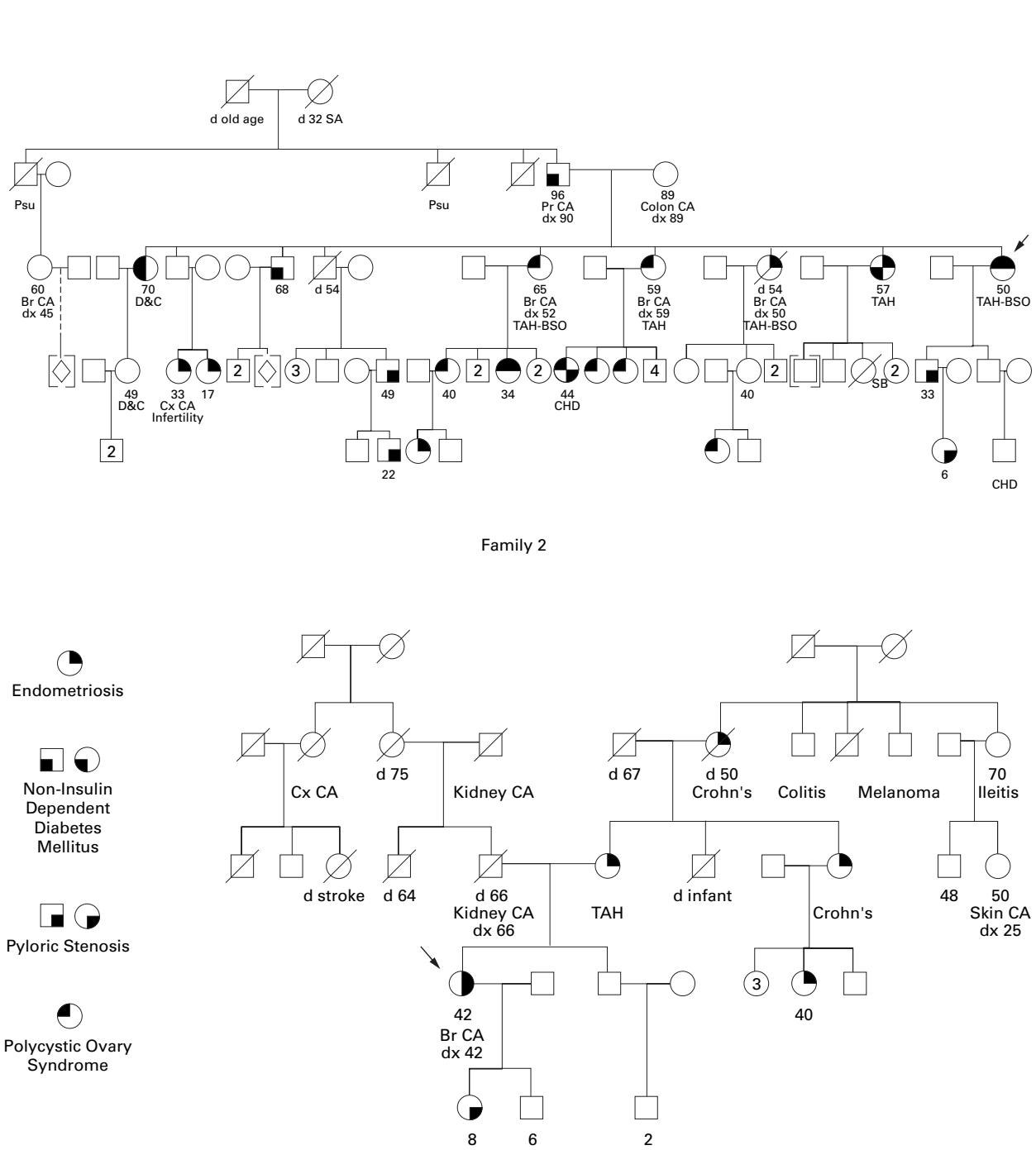

Figure 1 Pedigrees of families 1 and 2. Proband is indicated by an arrow. The age of the subjects appears directly below symbol. CA = breast cancer followed by age of diagnosis (dx); Psu = primary site of cancer was not known; Pr CA = prostate cancer; Cx CA = cervical cancer; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; NIDDM = non-insulin dependent diabetes mellitus; CHD = congenital heart disease; D&C = dilatation and curettage; SA = spontaneous abortion; SB = stillbirth.

each condition. A future study of pyloric stenosis in a case-control design may investigate any association with breast cancer or endometriosis.

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Punctate calcification of the epiphyses, visceral malformations, and craniofacial dysmorphism in a female baby

EDITOR—We report a fetus with striking craniofacial dysmorphism, brachydactyly, and cerebral and cardiac malformations in addition to punctate calcification of the epiphyses.

The mother was treated for tuberculosis seven years before the pregnancy but there were no known systemic illnesses or teratogenic influences during this pregnancy. The mother's first pregnancy resulted in a termination at 22 weeks of gestation for multiple congenital abnormalities, but further details are not known.

The baby was the second child born to a 21 year old mother. A termination was performed at 21 weeks of gestation because of multiple anomalies seen on antenatal scanning. Necropsy showed a female fetus (fig 1) with a weight of 1544 g, consistent with 17 weeks' gestation. The crown-heel length was 16.4 cm and right foot length was 18 mm. Facial examination showed an open right eye with exophthalmos, hypertelorism, a flat nasal bridge with hypoplasia of the alae nasi, flattening of the midface, a short philtrum with a well defined philtral groove, large lips, and a wide mouth with micrognathia. The right ear was simple and low set and the left ear was rudimentary

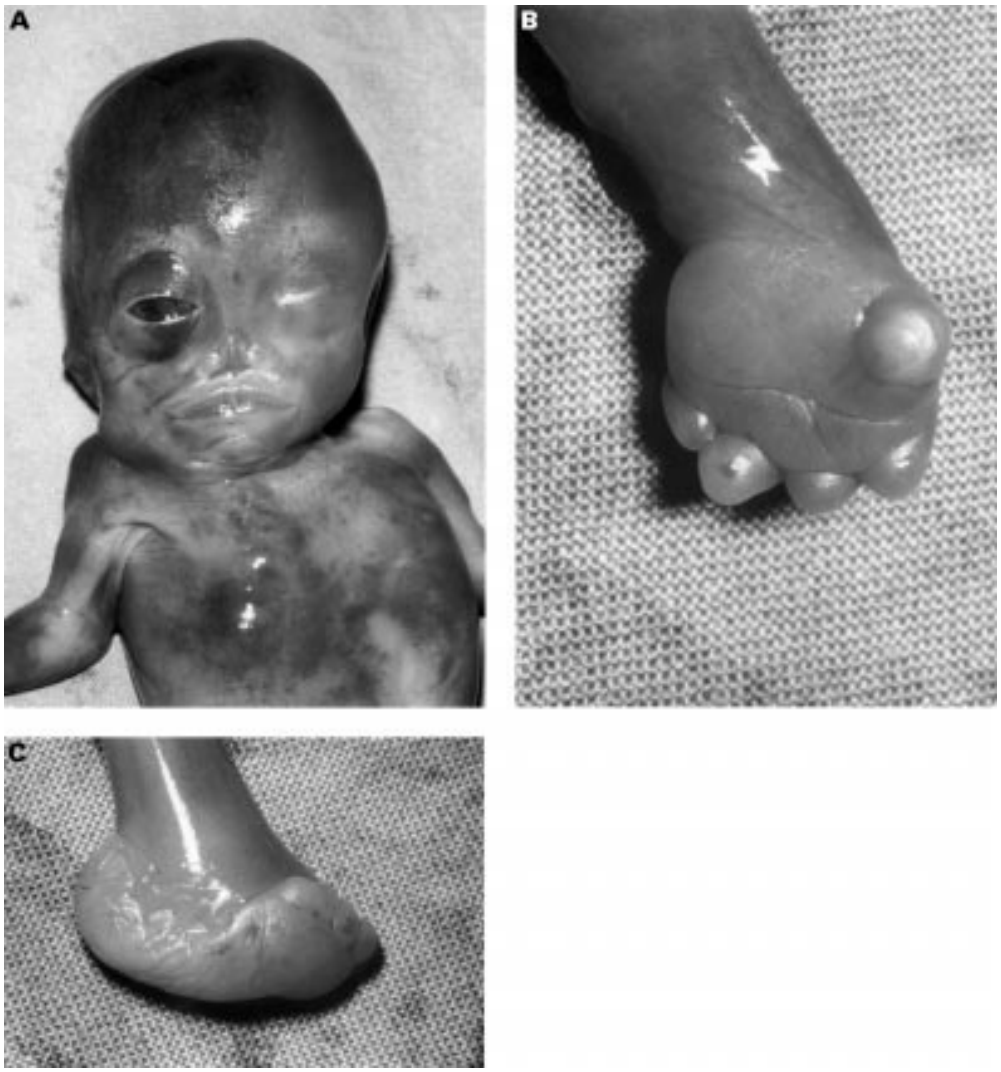

Figure 1 (A) Front view of fetus. (B) Hand of fetus. (C) Foot of fetus.