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Transmission of a Fragile X full mutation from a premutation male to his two daughters. P.J. Bridge[1], L.S. Dimnik[1], J.E. Chernos[1], J. Wages[2], W. Bloch[2] and D.R. McLeod[1]. Department of Medical Genetics[1], University of Calgary, Calgary, Alberta, Canada and Applied Biosystems Inc.[2] Foster City, CA.

A 10 year old female patient with developmental delay was tested for Fragile X syndrome. When she was found to have a mutation, we requested a blood specimen from her mother and recommended specific genetic counselling. When the mother was shown to be a non-carrier of Fragile X (19 and 23 repeats), we pursued the rest of the family and found another mutation in her older sister, a normal allele in her brother and a premutation in her mentally normal father. Mutations have been tested by a complementary combination of Southern blot, radiolabelled triplet repeat sizing when possible, and complete mutation analysis using a newly developed Applied Biosystems Inc. kit. The premutation in the father has 114 repeats. Fibroblasts and sperm from the father confirm the presence of only a premutation. The mutations in both daughters are mosaic smears extending from the top end of the premutation range well into the full mutation range. Both daughters have a further unusual feature in that approximately half of the mutant alleles are unmethylated. This leads to the rare appearance of a mitotically-unstable smear below the inactive X chromosome band (5.1 kb on Southern blot) as well as the smear in the usual position above this 5.1 kb band.

We believe that this is the first case of a Fragile X premutation expanding to a mutation when transmitted from a male to his daughter. This case obviously has important repercussions for the counselling of families with Fragile X syndrome.

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Genetic analysis of patients with pancreatitis and a history of alcohol abuse. K.G. Monaghan, C.E. Jackson, and G.L. Feldman. Henry Ford Hospital, Detroit, MI.

Hereditary pancreatitis (HP) is a rare, early-onset autosomal dominant genetic disorder characterized by epigastric pain and often more serious complications. Mutations have been identified in the cationic trypsinogen gene in patients with HP and in the cystic fibrosis transmembrane regulator (CFTR) gene in patients with HP and chronic pancreatitis. Pancreatitis can be induced by exposure to certain environmental factors, such as alcohol, although not all persons exposed will develop symptoms of the disease. We hypothesized that this phenomenon is due to a genetic predisposition in persons with pancreatitis attributed to alcohol abuse. We obtained informed written consent for participation in this study. We collected blood samples from 64 patients with a discharge diagnosis of pancreatitis. Review of the medical record and patient interviews were used to ascertain the phenotype, etiology of pancreatitis and to determine whether there was a family history of pancreatitis. Forty-six patients (34 African American, 11 Caucasian and 1 Hispanic) had either alcohol-induced pancreatitis or had pancreatitis and a history of alcohol abuse. 6 patients (13%) reported a family history of pancreatitis in at least one first-degree relative. Sequence analysis for the 5 exons and flanking intronic sequences of the cationic trypsinogen gene identified several unreported intronic polymorphisms which are most likely of no clinical significance but did not identify any novel or previously reported mutations. We screened for 39 CF mutations which account for approximately 90% of CF mutations in individuals of Northern European descent and 67% of African American mutations. The ΔF508 CF mutation was identified in 2 Caucasian patients (18%) and a previously unreported missense mutation in exon 19 of the CFTR was identified in an African American patient (3%). The significance of this novel mutation with respect to CFTR function is not known. The carrier frequency for CF mutations is 4% for Caucasians and 1.4% for African Americans. Analysis of the CFTR "5T" allele is in progress. Although our sample size is small, these results suggest that screening for cationic trypsinogen mutations will not be useful in identifying patients with alcohol-related pancreatitis. However, because the carrier frequency for CF mutations in patients with pancreatitis and alcoholism is increased above the population carrier frequency, these studies suggest a possible role of the CFTR in alcohol-related pancreatitis.