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High Frequency of Cystic Fibrosis Transmembrane Regulator Mutation L997F in Patients with Recurrent Idiopathic Pancreatitis and in Newborns with Hypertrypsinemia

To the Editor:

Cystic fibrosis (CF) (MIM 219700) is a genetic disease with multisystem involvement and in which defective chloride transport across membranes causes dehydrated secretion. The protein encoded by the CF gene (CFTR) is a transmembrane conductance regulator. The ability to detect CFTR mutations has led to the recognition of its association with a variety of conditions, including bronchiectasis, sinusitis with polyps, and male infertility (Estivill et al. 1996). A high frequency of mutations in the CFTR has more recently been shown in patients with chronic idiopathic pancreatitis (Sharer et al. 1998) and in newborns with hypertrypsinemia (Castellani et al. 1999). The exocrine pancreas is almost invariably affected in CF, even if not always with clinical manifestations (Lebenthal et al. 1993). In CF and in idiopathic pancreatitis, the earliest pathological finding is probably pancreatic ductular obstruction due to inspissated secretions (Oppenheimer et al. 1975; De Angelis et al. 1992). Hypertrypsinemia is thought to derive from pancreatic ductular obstruction and leakage of trypsinogen into the bloodstream (Crossley et al. 1979). Therefore, we postulated that there might be particular CFTR gene mutations involved in pancreatic ductular obstruction, as manifested in idiopathic pancreatitis or in neonatal hypertrypsinemia. Since routine CF mutation testing may miss rare gene alterations that can occur in these CF-related pathologies, a complete screening of the CFTR gene was performed in a group of 32 patients with idiopathic pancreatitis (14 of whom carried a CF mutation—the 5T variant—or borderline sweat chloride level, and 18 of whom were without common CF mutations or any other CF characteristic) and in 49 newborns with hypertrypsinemia and normal sweat chloride (32 of whom had a common CF mutation [some of these reported by Castellani et al. 1999], and 17 of whom did not have a common CF mutation). The 27 exons of the CFTR gene and their intronic flanking

regions were analyzed by denaturing gradient-gel electrophoresis (DGGE) and by automatic sequencing, as described elsewhere (Bombieri et al. 1998).

Aside from some common CFTR mutations, none of which appeared to be more represented than expected, in comparison with the CFTR gene mutation distribution in CF patients in the same population, rare mutations were found in 9 of 32 patients with idiopathic pancreatitis and in 21 of 49 newborns with hypertrypsinemia. Among these rare mutations, L997F was identified in 4 (12.5%) of 32 patients with idiopathic pancreatitis (genotypes L997F/ Δ F508, L997F/5T, and twice L997F/no mutation identified, respectively), and in 4 (8%) of 49 newborns with hypertrypsinemia (genotypes L997F/G542X, L997F/R553X, L997F/ Δ F508, and L997F-F1052V phase unknown, respectively). The cumulative frequency of the L997F mutation in pancreatic dysfunction (8 [9.87%] of 81) is significantly higher than that found in normal control individuals (Bombieri et al. 1998, 2000, and unpublished data) from the same population (3 [0.97%] of 315; Fisher's exact test, $P = .0002$; odds ratio 11.397 [range 2.95–44.029]). L997F is a highly conserved residue in transmembrane domain 9 among five species analyzed (Tucker et al. 1992). L997F was initially reported as a DNA variant (Fanen et al. 1992) and was described in a 5-year-old boy from northern India who presented a borderline sweat chloride value and features highly suggestive of CF (Cystic Fibrosis Genetic Analysis Consortium) and in patients with disseminated bronchiectasis (Bombieri et al. 2000, Girodon et al. 1997). Following the guidelines of a recent consensus statement on the diagnosis of CF (Rosenstein et al. 1998), we tested for L997F in 100 carriers of mutation Δ F 508 (mothers of typical patients with CF) from the same population as the individuals with pancreatitis and hypertrypsinemia; since none of them carried it, L997F is designated as a CF-causing mutation, according to criterion number 4 in the above-cited article (Rosenstein et al. 1998). This classification implies that the L997F heterozygotes compounded with common CF mutations found among the patients with idiopathic pancreatitis (Δ F508) and that the hypertrypsinemic newborns with negative sweat chloride (Δ F508, G542X, and R553X) should be diagnosed as affected by an atypical form of CF; a close follow-up is indicated for these patients. In conclusion, these data indicate that CFTR

L997F is associated with increased susceptibility to pancreatic ductular obstruction.

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Cystic Fibrosis Genetic Analysis Consortium, <http://www.genet.sickkids.on.ca/cftr>

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim> (for CF [MIM 219700])

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On the Age of the Most Prevalent Gaucher Disease–Causing Mutation, N370S

To the Editor:

We have recently described a common origin for the most prevalent mutation (N370S) observed among Gaucher disease (GD) patients of Ashkenazi Jewish (AJ) and Spanish descent (Díaz et al. 1999). We also estimated the age of this mutation, using a formula described by Risch et al. (1995b). Unfortunately, as R. Colombo pointed out in a recent report (Colombo 2000), there was an error in the formula presented in the original publication that was never rectified. In a reply (Risch et al. 1995a) to criticisms raised by Zoosmann-Diskin (1995), Risch et al. made no mention of an error in the formula. The continued application of the formula by researchers who may not be well versed in the field may lead to repeated mistakes if the error remains uncorrected. We apologize for our failure to recognize the error, but we are pleased that it has been identified by Colombo, who had no difficulty in re-estimating the age of the mutation, using our data. This