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Unique Frequency of Known Mutations in Brazilian MPS I Patients

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The frequency of 10 known mutations in the *IDUA* gene—Q70X, A75T, H82P, R89Q, 678-7 g→a, L218P, A327P, R383H, W402X, and P533R—was estimated in a group of 24 index cases with mucopolysaccharidosis type I. Three affected relatives were also analysed. Six of the 10 mutations screened were present in our patients (Q70X, R89Q, A327P, R383H, W402X, and P533R). These mutations account for 54% of the alleles; 37% of the genotypes were defined. Frequencies of these mutations are markedly different from those in the literature. A novel combination Q70X/A327P is described. This was the first time Brazilian MPS I patients were analysed with molecular techniques. The low frequency of common mutations indicates that a more comprehensive analysis of the *IDUA* gene should be done to delineate the mutation profile of MPS I better in our population. Am. J. Med. Genet. 90:108–109, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Mucopolysaccharidosis type I (MPS I, MIM 252800) is a lysosomal storage disease that presents three clinical manifestations: MPS IH or Hurler's syndrome (severe form), MPS IS or Scheie's syndrome (mild form), and MPS IH/S or Hurler-Scheie's syndrome (intermediate form) [Hopwood and Morris, 1990; Neufeld and Muenzer, 1995]. Isolation and cloning of the *IDUA* gene by Scott et al. [1990] led to the identification of about 50 different disease-causing mutations, including the common European mutations W420X and Q70X [Scott et al., 1995].

Our service is a reference laboratory for lysosomal storage diseases (LSDs) in Brazil, receiving samples from all over the country. Since 1982 we have diagnosed 62 patients with MPS I, corresponding to 11.8% of all LSD diagnosed. The incidence of the disease in the city of Porto Alegre between 1992 and 1996 was estimated to be 1:59,000 live births. However, this may be an underestimation due to the short period of time considered and to the possibility that some cases may be still undiagnosed or unregistered in the reference service.

MATERIAL AND METHODS

We analysed 24 unrelated MPS I patients diagnosed at the Medical Genetics Service of Hospital de Clínicas de Porto Alegre as described elsewhere [Leistner and Giugliani, 1998]. Patients were from different regions of Brazil and had different ethnic backgrounds and clinical phenotypes. Four of the 27 patients were classified as Hurler patients, 10 had intermediate phenotypes, seven were Scheie patients, and six had unassigned subtypes.

All patients were analysed for the presence of 10 known mutations in the *IDUA* gene: Q70X, A75T, H82P, R89Q, 678-7 g→a, L218P, A327P, R383H, W402X, and P533R [Scott et al., 1995]. Mutation detection was performed by restriction digestion of polymerase chain reaction products (Table I).

RESULTS AND DISCUSSION

Six of the 10 mutations analysed in the 24 index cases (48 alleles) were present in our cases, and their frequency is described in Table I. Only 37% of the genotypes were defined using this approach.

The Q70X mutation was present in only one patient whose other allele was A327P. This is the first time this genotype is described. The patient was 3 years old, showing neither short stature nor intellectual impairment. Language development was around 2 years but

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TABLE I. Frequency of the 10 Mutations Analysed in this Study and Restriction Enzymes Used for Detection

Mutation	Number of alleles	Frequency (%)	Restriction enzyme	Reference
W402X	10	20.8	*Bfa*I	Moskowitz et al., 1993
P533R	9	14.5[a]	*Msp*I	(Meaney, pers. comm.)
A327P	4	8.3	*Hha*I	Bunge et al., 1994
Q70X	1	2.1	*Sau96*I	Vellodi et al., 1997
R89Q	1	2.1	*Msp*I	Vellodi et al., 1997
R383H	1	2.1	*Hha*I	Bunge et al., 1994
A75T	0	0	*Hph*I	Clarke et al., 1994
H82P	0	0	*Hph*I	Clarke et al., 1994
678-7g→a	0	0	*Hae*III	Moskowitz et al., 1993
L218P	0	0	*Msp*I	Bunge et al., 1994

[a]Two homozygous patients were born to consanguineous parents.

myringotomy was performed at the age of 2 years and 8 months. Whether central nervous system function may decline with age cannot be predicted, but we would rather classify this patient as having a Hurler-Scheie phenotype.

The reported frequencies for Q70X and W402X are markedly higher in patients of Anglo-Saxon origin, reaching frequencies of 46% for W402X and 15% for Q70X, as reported by Scott et al. [1992a, 1992b], and Clarke et al. [1994]. These mutations seem to be less frequent among Italian patients. Gatti et al. [1997] reported a frequency of 13% for Q70X and 11% for W402X. The authors also mention another common mutation, P533R, with a frequency of 11%, which also seems to be frequent in Spain [Coll et al., 1997]. Coll et al., [1997] reported a frequency of 10% for P533R, 10% for Q70X and 60% for W402X in Spanish patients. If we assume that Brazilian patients are genetically closer to Spanish and Italian patients than to Anglo-Saxon patients, we should still consider the incidence of Q70X in our population extremely low. The frequency of W402X (20.6%) is slightly higher than the frequency found among Italian patients (11%) and much lower than the Spanish frequency (60%) for this mutation. Nevertheless, the P533R mutation was found in a significant portion of our patients, as expected. Also, A327P, a common mutation in Central Europe and Germany, was the third most frequent in our sample, reflecting the ethnic components of the Brazilian patients.

Mutations Q70X, P533R, A327P, and W402X often are related to the severe form of the disease, although they can be found in heterozygous state in patients with milder phenotypes. In our study, of the 10 index cases who were heterozygous for W402X and had their phenotype assigned, 3 have the mild form of the disease, 3 have the intermediate form, and 2 have the severe form. Mutations associated with mild phenotypes, such as R89Q and 678-7 g→a, are absent or extremely rare in our sample. Therefore, there is probably another mutation that accounts for the milder phenotype of three of our Scheie patients who are heterozygous for W402X. It is impossible to predict whether there is a common mutation for all the Scheie patients or if they bear exclusive mutations. Anyway, it is remarkable that there is an increase in the number of patients with milder forms of the disease in our population.

This is the first report on molecular genetics of MPS I in Latin America. The unexpected low frequency of common mutations of the *IDUA* gene indicates that a more comprehensive analysis of these patients is needed. This must comprise not only a molecular screening for other known mutations, but also a complete screening for new mutations. In addition, a comprehensive clinical and epidemiological investigation could help assign the ethnic background of these patients and aid understanding of the genotype-phenotype correlation.

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