Molecular study of the gene for alpha-L-iduronidase. Characterization of mutations in patients with mucopolysaccharidosis type I and polymorphisms in the Czech population.

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disorder caused by a deficiency of alpha-L-iduronidase (IDUA, E.C 3.2.1.76), which is involved in breakdown of dermatan and heparan sulfates within the lysosome. MPS I is inherited in an autosomal recessive manner. During the last 25 years the diagnosis of MPS I was proved enzymatically in 19 patients from Czech and Slovak populations. Fifteen of them had severe Hurler syndrome, 2 had least severe Scheie syndrome and two had the intermediate Hurler/Scheie phenotype.

We performed the mutation analysis in 17 Czech and Slovak MPS I patients and found 32 mutated alleles with a high prevalence of null mutations W402X (11/34) and Q70X (7/34). Three of eleven mutations were novel (V620F (3/34), W626X (1/34) and E640fs (2/34)). In addition, we followed 13 known polymorphisms, which were used for haplotype determination in most mutant alleles. Frequencies of five of these polymorphisms (A8, A20, Q33H, L118 a R105Q) and haplotypes derived from these/their nucleotide changes were determined in control population. The novel mutations together with another mutation D315Y, which was not studied previously, were characterized by transient expression studies in CHO cells. All mutations but one (E640fs) caused a severe reduction of expressed enzyme activity. The residual activity found in the E640fs corresponds to the milder phenotype of patients carrying the allele. Definite accordance seems to be in patients homozygous for the prevalent alleles W402X or Q70X. Prediction of phenotype from other combinations is complicated and is discussed in the thesis.

Kľúčové slová:

Mukopolysacharidóza typu I, alfa-L-iduronidáza, Hurlerovej syndróm, Scheieov syndróm, mutácie, polymorfizmy, haplotypy, genotyp-fenotypová korelácia

Mucopolysaccharidosis type I, alpha-L-iduronidase, Hurler syndrome, Scheie syndrome, mutations, polymorphisms, haplotypes, genotype-phenotype correlation