A novel iduronate 2-sulfatase mutation in a Chinese family with mucopolysaccharidosis type II

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Background: **Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is an X-linked multisystem disorder resulting from the defective activity of the enzyme iduronate-2-sulfatase (IDS). Genetic testing is crucial in clarifying and diagnosing different types of MPS diseases. In this paper we report a novel IDS nonsense mutation resulting in MPS II in several patients from a Chinese family.**

Methods: **IDS enzyme activity, polymerase chain reaction, and DNA sequencing were performed to confirm the diagnosis of MPS II.**

Results: **Three patients had no detectable IDS activity. Two genetic tests revealed a novel IDS nonsense mutation (c.1030G>T, p.E344X) inherited from their mothers. The nonsense mutation shortened the peptide chain from 550 to 344 amino acids, which is believed to be a disease-causing mutation.**

Conclusions: **MPS II is inherited in an X-linked manner. The risk to sibs depends on the carrier status of the mother. Genetic testing is necessary to identify disease-causing mutation. With this information, carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk become possible.**

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Key words: **iduronate 2-sulfatase gene; mucopolysaccharidosis II; mutation**

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Introduction

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is an X-linked multisystem disorder caused by a deficiency in IDS activity. The disorder is characterized by glycosaminoglycan (GAG) accumulation. MPS II has an incidence of approximately 0.31 to 0.71 per 100 000 live births.[1] The vast majority of affected individuals are male, and to date, very few female patients with MPS II have been reported. Disease phenotypes in most females with MPS II are due to the inherited IDS gene mutation from the mother with preferential inactivation of the non-mutant paternal alleles.[2] The clinical spectrum of MPS II varies significantly and includes mild, intermediate, and severe variants according to the age of onset, disease severity, and rate of progression. Urine GAGs, skeletal survey, and IDS enzyme activity facilitate the diagnosis of MPS II. However, genetic testing for IDS is necessary for the male patients who present unusual phenotypes or phenotypes that do not match the results of GAG tests. Furthermore, the identification of IDS mutation is important for genetic counseling and prenatal diagnosis. In the current report we present three male patients (all of whom are cousins) with MPS II resulting from a nonsense IDS mutation.

Case reports

Clinical information

Proband: A 4-year-old boy who had been experiencing abdominal distension and diarrhea for one month was brought to our clinic. Physical examination showed that his liver was 10 cm below the right costal margin in the mid-clavicular line, with a firm, sharp margin. His spleen was 8 cm below the left costal margin in the midclavicular line. He suffered from a coarse face, including prominent supraorbital ridges, a broad nose and nasal bridge, large rounded cheeks, thick lips, and such features as a short neck and small stubby fingers. He was born normally to non-consanguineous parents. The development of his psychomotor and speech was delayed, and he experienced an increased frequency of recurrent respiratory infections. Magnetic resonance

Case report

imaging revealed encephalatrophy.

Patient 2: A 5-year-old boy, an older cousin of the proband, was brought to our clinic owing to a similar coarsening of the facial features. Patient 2 also suffered from hepatosplenomegaly and navel hernia. His developmental progress was slow. Anteroposterior and lateral X-rays of the chest showed wide ribs with tapered posterior ends and a paddle appearance.

Patient 3: A 1 year and 4 months old boy, a young cousin of the proband and patient 2. He did not have the typical coarsening of facial features. Physical examination showed that his head circumference was 48 cm. In addition, his ribs had a similar outer border. His liver and spleen were only slightly enlarged, and there was a large piece of cyan birthmark on his back. He had inguinal hernia. The boy had febrile convulsions twice when he was just nine months old. He was born by uterine-incision delivery because of oligohydramnios. However, this patient did not have a history of poor oxygen or asphyxia. To date, his growth development is normal for his age.

IDS activity and gene testing

Enzyme assay for iduronate sulfatase showed that the three patients had no detectable IDS activity. Genetic tests were performed on the proband and patient 2. The results showed a novel nonsense mutation (c.1030G>T, p.E344X) inherited from their mothers (Fig.). Mutation E344X caused the elongation of the amino acid chain to stop at position 344; thus, the mutation was believed to be disease causing. Although genetic analysis was not performed on patient 3, it was assumed that he might have had the same mutation. The other family members refused to undergo the genetic analysis. Thus, other carriers and patients may exist within the family.

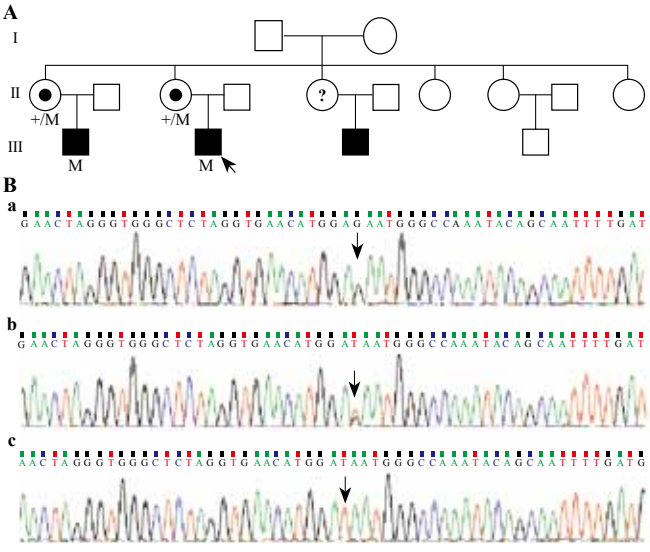

Fig. Pedigrees and genetic analysis of patients with IDS mutations. **A:** Pedigrees of affected family with novel IDS mutation (proband indicated by arrow); shaded square indicates affected individuals; +/M: individual carrying heterozygous IDS mutation; M: male individual carrying IDS mutation. **B:** Chromatograms of IDS mutations, in comparison with normal sequence and heterozygous IDS mutation carrier. Arrows indicate the occurrence of mutations. a: control; b: mother; c: patient.

Discussion

MPS II, inherited in an X-linked recessive manner, is a lysosomal storage disorder caused by IDS deficiency. In the present study, we present three patients who are cousins and have similar symptoms, including distinctive facial appearance, hepatosplenomegaly, moderate mental retardation, recurrent respiratory infections, and skeletal deformities. The clinical spectrum of MPS II varies greatly, and involves the central nervous system (CNS). The severe form of the disorder is characterized by progressive mental retardation, physical disability, severe airway obstruction, skeletal deformities, and cardiomyopathy resulting in death in the first or second decade of life. The CNS of patients with a mild form of MPS II is minimally affected or not at all. However, the effect of GAG accumulation on the other systems may be similar to that in the severe form. The gold criterion for diagnosis of MPS II is detecting activity of IDS enzyme, while gene testing is essential, especially in young patients and those who present atypical phenotype or one that does not match the results of GAG testing.

The human IDS gene (MIM 300823) is located in Xq28 and contains nine exons spanning approximately 24 kb chromosome regions. IDS is the only gene associated with MPS II, thus playing a pivotal role in its diagnosis. Using a direct sequencing method, we identified an IDS nonsense mutation c.1030G>T, p.E344X resulting in IDS deficiency in the three patients. A search in the Human GeneMutation Database (HGMD, http://www.hgmd.org/) confirmed this nonsense mutation to be a novel case first reported in the present study. To date, more than 350 IDS mutations have been found, including exonic point mutations comprising half mutations, followed by exonic and whole-gene deletions, complex rearrangements, and gross insertions/duplications.

In a large collection of Chinese patients with MPS II, Zhang et al[3] identified many different mutations, of which the most frequent mutations are also exonic point mutations. In addition, a synonymous mutation c.879G>A (p.Gln293Gln) was identified in a female patient with MPS II, which resulted in loss of the original splicing site, activated a cryptic splicing site

upstream, leading to a 28 bp deletion and a premature termination at p.Tyr285GlufsX47. Together with concurrent skewed X-inactivation this synonymous mutation (p.Gln293Gln) was believed to facilitate the development of MPS II in this girl. Otherwise, IDS mutations from this largest cohort of Chinese patients are frequently located in exon 9, next to exon 2, and against exon 3. These results, however, are different from those of foreign studies, indicating that the IDS gene has high genetic heterogeneity, and the mutation patterns of patients from different races, nations and areas are diversified.

In general, the IDS genotype correlates with the clinical phenotype. Boys with a complete absence of functional enzymes owing to gross IDS gene changes, for example, large deletions and gene-pseudogene rearrangements, invariably manifest severe CNS symptoms.[4] Regarding IDS point mutations, a significant genotype-phenotype correlation has yet to be established. In the present study, the nonsense mutation c.1030G>T, p.E344X resulted in an intermediate phenotype. Missense mutations are associated with the severe, intermediate, or attenuated phenotype.[5] Furthermore, previous studies have reported two siblings with the same IDS mutations, in which one brother displays severe symptoms, whereas the other presents attenuated symptoms.[6,7] Other factors are more likely to modify the IDS effects on the clinical presentation.

Treatment of MPS II is symptomatic and palliative, based on the coordination of diverse medical specialties. Although the treatment for MPS II with hematopoietic stem cell transplantation has been proposed in the 1980s, the results are not considered satisfactory.[8] In 2006, enzyme replacement therapy (Elaprase) was approved for clinical use for MPS II.[9,10] Most of the clinical trials studied the effect of Elaprase on patients with relatively attenuated symptoms.[11] However, no information on the outcome of Elaprase on individuals with severe CNS disease is currently available. In addition, the high price of Elaprase limits its use in China. Thus, MPS II remains an important social and economic concern.

In summary, we found a novel IDS nonsense mutation in two related patients who were cousins. Identifying IDS mutations is important for the genetic counseling and prenatal diagnosis in affected families. Genetic counseling can provide families with information about reproductive risks. Thus, this method can be used to make a prenatal diagnosis for pregnant women at high risk of MPS II, and it can also contribute to the prevention of MPS II occurrence.

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References

1 Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 2005;28:1011-1017.
2 Tuschl K, Gal A, Paschke E, Kircher S, Bodamer OA. Mucopolysaccharidosis type II in females: case report and review of literature. Pediatr Neurol 2005;32:270-272.
3 Zhang H, Li J, Zhang X, Wang Y, Qiu W, Ye J, et al. Analysis of the IDS gene in 38 patients with Hunter syndrome: the c.879G>A (p.Gln293Gln) synonymous variation in a female create exonic splicing. PLoS One 2011;6:e22951.
4 Wraith JE, Beck M, Giugliani R, Clarke J, Martin R, Muenzer J. Initial report from the Hunter Outcome Survey. Genet Med 2008;10:508-516.
5 Muenzer J, Beck M, Eng CM, Escolar ML, Giugliani R, Guffon NH, et al. Multidisciplinary management of Hunter syndrome. Pediatrics 2009;124:e1228-e1239.
6 Yatziv S, Erickson RP, Epstein CJ. Mild and severe Hunter syndrome (MPS II) within the same sibships. Clin Genet 1977;11:319-326.
7 Martin R, Beck M, Eng C, Giugliani R, Harmatz P, Munoz V, et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics 2008;121:e377-e386.
8 Wraith JE, Scarpa M, Beck M, Bodamer OA, De Meirleir L, Guffon N, et al. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr 2008;167:267-277.
9 First treatment for Hunter syndrome. FDA Consum 2006;40:5.
10 Treatment for Hunter syndrome approved. FDA Consum 2006;40:4.
11 Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006;8:465-473.

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