Journal of Rare Diseases Research & Treatment

Mini-Review Open Access

Mini-review on "Molecular diagnosis of 65 families with mucopolysaccharidosis type II (Hunter syndrome) characterized by 16 novel mutations in the IDS gene: Genetic, pathological, and structural studies on iduronate-2-sulfatase."

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Article Info

Article Notes
Received: November 29, 2016
Accepted: December 28, 2016

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ABSTRACT

Mucopolysaccharidosis type II (MPS II; Hunter syndrome; OMIM #309900) is an X-linked congenital disorder characterized by an accumulation of glycosaminoglycans in the body. Accumulating evidence has suggested that the prevalence of the severe type of MPS II is almost 70%. In addition, novel mutations that are relevant to MPS II pathogenesis are being increasingly discovered, so the databases of genetic data regarding pathogenic mutations have been growing. We have recently reported a collection of 16 novel pathogenic mutations of the iduronate-2-sulfatase (IDS) gene in 65 families with MPS II in a Japanese population[1]. We also proposed that a homology-based prediction model, a computer-assisted method, is effective in estimating whether or not a mutation of interest may be associated with the severe type of MPS II. Overall, our results regarding genetic mutations of the *IDS* gene will provide a key to selection of the most appropriate therapeutic strategy, and will help to maximize the pharmacological outcome of currently available agents.

Introduction

Mucopolysaccharidosis type II (MPS II; Hunter syndrome; OMIM #309900) is an X-linked lysosomal storage disorder that is characterized by an accumulation of glycosaminoglycans, particularly heparan sulfate and dermatan sulfate, in the body[2,3]. Iduronate-2-sulfatase (IDS) is an enzyme responsible for MPS II, thus genetic testing of this enzyme has been recognized as vitally important in the molecular diagnosis of the disorder. It is known that MPS II has two disease subtypes, with differing levels of severity. The severe type of the disorder involves neuronal manifestations that are resistant to currently approved enzyme replacement therapy (ERT) via intravenous administration. In contrast, the attenuated type of MPS II leads to splenomegaly and other visceral phenotypes, but development of intellectual function is normal, thus the current ERT protocol has been favorably accepted in its treatment . Accumulating evidence has suggested that the ratio of severe to attenuated type of MPS II is approximately 2:1.

The *IDS* gene is 24-kb in size with nine exons, and is located at the Xq27/28 boundary. There is a genotype-phenotype correlation between MPS II disease severity and the pathogenic mutation in the *IDS* gene; thus an increase in the amount of related genetic data

has been anticipated for the prediction of occurrence of MPS II disease subtype. Previous studies indicated that MPS II is very common in Asian countries, such as Japan, Korea, China, and Taiwan[4-7]. In fact, such a disproportional distribution of disease-affected individuals has also been reported for other types of MPS - a well-known example is that of MPS VI in a Brazilian population[8]. Similarly, a high incidence of MPS III in Germany, the Netherlands, and Western Australia has also been described[9-11]. In addition to the *IDS* gene, which synthesizes an intact polypeptide of the IDS protein, there is a pseudogene termed *IDS-2*, which has no IDS enzyme activity. Thus, it has occasionally been noted that the recombination of *IDS-IDS-2* induces the severe type of MPS II[1]. A large deletion of the *IDS* gene has also been reported[1,7,12,13].

Pathogenic mutations in the *IDS* gene in a Japanese population

On the basis of the earlier studies, we classified the pathogenic mutations of the *IDS* gene for MPS II into six different categories, as follows: missense, nonsense, frameshift, recombination, splicing error, and other mutations that are not included in the preceding five categories[1]. In our study, the ratio of the severe to attenuated type of MPS II was 41:24, which is similar to the 2:1 ratio that has been suggested in previous studies[7,13-14] . In the present study, 87.5% (21/24) of pathogenic mutations in the attenuated type of MPS II (n = 24) involved missense mutations. In contrast, there was a variety of pathogenic mutations in the *IDS* gene in the severe type of MPS II (n = 41). The most frequently observed type of mutation was missense mutation (29%, 12/41), followed by recombination (17%, 7/41), nonsense (14%, 6/41), and frameshift (14%, 6/41), respectively.

Missense mutations

We identified 33 missense mutations in the *IDS* gene in 65 Japanese families. Of these, 64% (n = 21) were associated with the attenuated type of MPS II, whereas 36% (n = 12) were linked to the severe type. The number of missense mutations was the highest, compared to the other mutation categories, which is in accordance with the results of previous studies[7,13].

Nonsense mutations

Of the eight nonsense mutations identified in this study, 75 % (n = 6) were involved in the severe type, while 25 % (n = 2) were linked to the attenuated type of MPS II. In previous studies, nonsense mutations of the *IDS* gene have been almost equally found in both types of MPS II. For example, 50% (3/6) and 57% (4/7) of nonsense mutations were found in a Korean[13] and in a Chinese study, respectively[7].

Recombinations

Recombination is an occasionally observed pathogenic mutation of the *IDS* gene, and is closely associated with the pathogenesis of the severe type of MPS II. The presence of the *IDS-2* pseudogene near the *IDS* gene on the X-chromosome means that the recombination mutations found in MPS II most likely generate an *IDS-IDS2* recombination. In this situation, there is almost no remaining IDS enzyme activity. We consistently identified 100% (7/7) cases of recombination in the severe type of MPS II. This finding was supported by the results of previous studies, in which all cases of recombination mutation in a Korean study (1/1) and a Chinese study (4/4) were linked to the severe type of MPS II[7,13].

Frameshifts and splicing errors

Both of these types of mutation are rarely detected in MPS II. Essentially, each mutated *IDS* gene with frameshift and splicing error generates a truncated IDS protein; therefore virtually no residual enzyme activity is expected in these mutations. This is supported by the fact that we identified six cases of frameshift mutations and four cases of mutations with a splicing error, and all were found in the severe type of MPS II. This trend has also been consistently observed in other studies. For example, 81% (13/16) of frameshift mutations in a Korean study and 67% (2/3) such mutations in a Chinese study were involved in the severe type of MPS II.

Read-through: a mechanism of translation involved in nonsense mutation that leads to the attenuated type of MPS II

Basically, the nonsense mutation is closely associated with the severe type of MPS II, due to the premature termination of an intact IDS polypeptide. In addition, 25% (2/8) of patients with a nonsense mutation showed the attenuated type of MPS II. Read-through is a mechanism of translation of mRNA to protein that synthesizes a polypeptide based on mRNA, even if any of the termination codons (i.e., TAA, TGA, and TAG) appears as a nonsense mutation[15]. Thus, although nonsense mutations are generally linked to the severe type of MPS II, such mutations are occasionally identified in the attenuated type of the disorder if read-through occurs. We identified two read-through mutations of the *IDS* gene: c.22C>T (p.R8X) and c.1327C>T (p.R443X)[1]. Read-through can be enhanced in the presence of an antibiotics gentamicin and PTC-124[15]. It has been hypothesized that gentamicin may enhance the recruitment of tRNA for other amino acids.

Homology-based modeling

Homology-based modeling is a technique for the prediction of disease subtype, and is based on the alteration

of a nucleotide in nonsense mutations of the *IDS* gene[16]. This method identifies the number of dislocated atoms in both the main chain and side chains of the polypeptides, the root-mean-square distance (RMSD) values between the mutant and wild-type IDS proteins, and the accessible surface area of the IDS protein. A detailed study showed that the number of dislocated atoms and RMSD values in the severe type of MPS II was increased compared to the attenuated type[16]. This technique was used to study α–glucosidase for Pompe disease[17], α-L-iduronidase for MPS I[18], and β-glucosidase for GM1 gangliosidosis and Morquio B disease[19].

We reported the predicted structure of the P120R and N534I IDS mutant proteins together with wild-type IDS protein[1]. The P120R IDS mutant protein is involved in the severe type of MPS II, since numerous atoms in the amino acids of the polypeptide were dislocated. This observation was consistent with previous examples of proline-containing mutant proteins, in which any substitution of proline with another amino acid induces a large alteration of protein structure. In contrast, the N534I IDS mutant protein revealed a limited number of dislocated atoms in the amino acids of the polypeptide, suggesting that this mutant may be linked to the attenuated type of MPS II. These results raise the distinct possibility that homology modeling has the potential to predict disease pathogenesis, as induced by novel mutations of the *IDS* gene.

Future perspectives

Given that almost 70% of individuals with MPS II have the severe type of the disorder; it is important to have a solid therapeutic strategy in place with regard to the selection of an effective treatment for neuronal manifestations. Several therapeutic methods to efficiently deliver IDS enzyme into the brain are currently in development. For example, a preclinical study is using an antibody against human insulin receptor fused to an intact IDS enzyme, with the aim of penetrating the blood-brain barrier, thus we may expect an improved outcome with regard to neuronal manifestations of the severe type of MPS II[20]. Accumulating data have also shown that the identification of suspected disease via screening of newborns increases the opportunity for earlier initiation of an existing therapy[21]. Subsequent quantification of glycosaminoglycans, such as heparan sulfate and dermatan sulfate, using a sensitive method has also been reported[22,23]. These analytical techniques are expected to increase beneficial therapeutic outcomes. Thus, our data on the pathogenic mutations of the *IDS* gene may pave the way for evidence-based selection of therapeutic strategies for MPS II.

Acknowledgments

This work was supported by a grant-in-aid from the Japan Agency for Medical Research and Development to TO (15AeK0109050s0302), and a Grant-in-Aid for Scientific Research (C) to RM (16K08958).

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