Mucopolysaccharidosis VII: A case report and literature review.

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Abstract

Mucopolysaccharidosis VII (MPS VII) is a rare, genetic disease that is usually inherited as an autosomal-recessive trait. Genetic mutations affect mental retardation, skeletal deformities, corneal clouding, hepatosplenomegaly and intelligence. To date, several genes have been found in related to patients with MPS VII. Here, we used whole-exome sequencing to identify a mutation (NC_000007.13:g.65444706G>A) in GUSB gene in an eight year old boy with MPS VII. Subsequently, we speculated that the variant of GUSB gene is critical for the proper function of GUSB, and might had led to an absence of the β-glucuronidase or reduce activity of the enzyme.

Keywords: Mucopolysaccharidosis VII, Case report, Literature review, GUSB, Mutation.

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Introduction

Mucopolysaccharidosis VII (MPS VII) is a rare autosomal recessive condition classified in the group of mucopolysaccharide storage diseases [1]. It results from a deficient function of the enzyme β glucuronidase (GUS: b-D-glucuronoside glucuronosohydrolase, EC 3.2.1.31; GUSB; MIM 611499) [2,3]. Deficiency of beta-glucuronidase (GUSB) results in progressive accumulation of undegraded glycosaminoglycans (GAGs) in various tissues including the brain [3,4]. The accumulation of glycosaminoglycans may disrupt various processes of physiological and biochemical: the pathways related to gangliosides metabolism, receptor-mediated signaling, mechanisms related to the activation of inflammation, the intracellular and extracellular homeostasis of these macromolecules, oxidative stress and permeability of the lysosomal membrane, and alterations in intracellular ionic homeostasis and the endosomal pathway [5].

MPS VII was the first to be described in 1973 by Sly [6], and it is rare with the incidence rate 1/84000–1/130000 [7]. As an autosomal recessive hereditary disease, Mucopolysaccharidosis type VII usually occurs on the offspring of the marriage between first Cousins. The patients’ clinical manifestations are facial dysmorphism, skin coarse, diminutive, skeletal deformity, hepatosplenomegaly, retinal degeneration, stiff joints, cognitive deficits, hearing impairment and movement restricted [7,8]. At present, there is no special treatment for MPS VII. If we do not treat it, death will occur during adolescence. As a result, it poses a significant burden on society.

Humans [6], cats [9,10], dogs [11], and mice [12-14] have all been used as research models for MPS VII. Due to the complexity and severity of disease between MPS VII mice and Sly disease patients are similarity, MPS VII mice has been used extensively as a model system to study different therapeutic interventions [15]. According to the disease time and different degrees of severity, MPS VII can be classified as 3 sub-types. Subtypes I and subtypes II have severe phenotype and characteristics of early onset, manifests respectively on birth or within 4 years old. Their clinical performance are edema, multiple Skeletal malformations (dislocation of the hip joint contracture, thoracolumbar side after a sudden), giant deformity, coarse facial features, hepatosplenomegaly, inguinal hernia, navel hernia, recurrent upper respiratory tract infections, growth retardation, etc. Subtype III has mild manifestation and characteristics of late onset. Their clinical performances are mental retardation, and maculae corneae [16].

The 3 phenotypes appear to be caused primarily by different combinations of mutant alleles at the β-glucuronidase Glycosides Enzyme Gene (GUSB). The GUSB gene that
patient was diagnosed with Mucopolysaccharidosis VII at the age of 7 due to extremely severe mental retardation on account of abnormal growth and development. He and his parents came to Second Hospital Affiliated to Wenzhou Medical College on account of abnormal growth and development. In consideration that MPS VII is an inherited disease in family, variants in the individual were chosen for further analysis. Whole-genome exon sequencing results were screened out by the human gene bank dbSNP129, the international human genome haplotype map program (abbreviated HapMap program) exome data, and the exome data of 1000 genome projects. There were 1615 missense mutations and 297 deletions. Then, this study used ANNOVAR software to predict potentially harmful mutation sites to narrow down the candidate genes, used the GERP score to rank candidate genes for harmfulness, and focused on the genes which had been reported involving in Mucopolysaccharidosis VII of cats, dogs, mice and humans. The gene β-Glucuronidase (GUSB) has been reported to be related to MPSVII. It was first suggested that the candidate gene GUSB (NC_000007.13: g.65444706G>A) may be related to MPSVII. The coverage in the exome sequencing of the variant in GUSB was 35X and 191X. Using traditional Sanger sequencing to verify, no candidate gene GUSB (13: g.65444706G>A) mutation site was found in other members of the family. In addition, the mutation (NC_000007.13: g.65444706G>A) in GUSB have not been well characterized, but mutations in GUSB were found in Mucopolysaccharidosis VII patients by other researchers, and we therefore supposed this variant as a pathogenic mutation of this family.

**Mutation analyses**

β-Glucuronidase (GUSB) is a lysosomal enzyme. It’s important that GUSB in the normal step-wise degradation of glycosaminoglycans. GUSB is encoded by GUSB gene [20]. The β-glucuronidase is a lysosomal homotrimer [21], and comprised of 651 amino acid residues (78 kD) [22]. The GUSB monomer is comprised of three distinct structural domains. The first domain is a jelly roll shape, which is highly distorted and forms a barrel-like structure along with two b-hairpin insertions. The hairpin loop of the jelly roll motif was considered to be an essential part of GUSB for lysosomal

**Whole exome sequencing**

Whole-exome sequencing and analysis protocols was developed by the Human Genome Sequencing Center at the Baylor College of Medicine [18]. Briefly, genomic DNA samples were fragmented with the use of sonication, ligated to Illumina multiplexing paired-end adapters, amplified by means of a polymerase-chain-reaction assay with the use of primers with sequencing barcodes (indexes), and hybridized to biotin-labeled VCrome (version 2.1) [19]. The exomes of the patient (IV: 5) were captured and sequenced. The average sequence read depth was 81X in targeted exons. Sequencing data was aligned to the NCBI human reference genome (NCBI build 37) and compared to NCBI Single nucleotide variation detection (dbSNP) Build 132, 1000 Genomes Project, HapMap project and YH data-base. A total of 1912 genetic variations, including nonsynonymous mutations, splice-acceptor and splice-donor site variations, and Insertion deletion site detection (InDels), were identified from the individual (IV: 5) in the Mucopolysaccharidosis VII family.

Case Report

**Patient**

Clinical data was collected through the parents of patient interviews, medical records, and physical examinations. The patient with stunting, walking instability, mental retardation, forehead convex eyebrows thick, low nose, wide eyes, thick breathing, corneal slightly turbid, sluggish eyes, sleep snoring, mouth shape, weak vision, sparse teeth. The clinical details of the radiographically unaffected gene carriers and affected gene carriers in the MPS VII family were shown in Figure 1. The proband (IV: 5) of the MPS VII family, the son of a consanguineous parent, was a 7 year old boy. This boy was the first child of healthy parents. And he has a normal younger sister. He was born at term with normal length and weight. He proband (IV: 5) of the MPS VII family, the son of a consanguineous parent, was a 7 year old boy. This boy was the first child of healthy parents. And he has a normal younger sister. He was born at term with normal length and weight. He...
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Mucopolysaccharidosis VII is a disease caused by accumulation of GAGs due to lysosomal defects, the incidence of which is 1/840000-1300000 [7]. In China, the first MPS VII was reported in 2011 by Huang et al [7]. They found that the patient with MPS type VII was a 2 months baby boy. The boy was mainly characterized by edema, liver splenomegaly, oblique hernia and decreasing platelets. The urine excretion of patient significantly increased, and patient finally was definited as MPS VII phenotype. It is interesting to note that no mutation in active-site residues Glu540, Glu451, or Tyr504 was reported in MPSVII patients. Among these, the truncating mutation of Trp507X produces a more severe MPSVII phenotype. A comprehensive analysis of structural changes with respect to mutation sites have already been reported earlier [30,31].

Gitzelmann et al. [32] found a pathogenic mutation (c.155C>T) only in their case of MPS VII. The c.155C>T mutation was located in exon 1. And it was predicted that the phenotypic severity in MPS VII patient was predominantly influenced by the c.155C>T mutation, which caused total destruction of β-glucuronidase enzyme activity in transfected cells. In addition, another mutation (c.1120C>T) had been further detected in one allele of a German proband before [33]. The c.1120C>T mutation might have led to an absence of the mental retardation because the c.1120C>T mutation led to β-glucuronidase a residual activity of 5.5% compared with the wild type [34].

In our case, the mutation which we hadn’t found in previous studies was heterozygotes. The mutation (G was substituted by A) had led to threonine change into serine. And we speculated that the variant of GUSB (NC_000007.13:g.65444706G>A) was a missense mutation in the proband. The identified variant of GUSB (NC_000007.13:g.65444706G>A) was a missense mutation in the proband. In the position 65444706 of chromosome 7, G was substituted by A, which led to change of amino acid.

Discussion

Type VII mucopolysaccharides disease is known as Sly syndrome, which is the most recently recognized mucopolysaccharidosis associated with β-gluconidase deficiency [3]. The disease is caused by beta-D-glucuronidase deficiency. Deficiency of GUSB causes partial degradation of Heparan Sulfate (HS), Chondroitin Sulfate (CS), Dermatan Sulfate (DS). Degradants accumulate in the lysosomes of many tissues, which lead to cell damage and organ dysfunction [23,26].

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Mucopolysaccharide VII disease is caused by a loss of lysosomal hydrolase activity due to a mutation in the β-glucuronidase gene. Mutation of β-glucuronidase gene (GUSB MIM #611499) have been described in many species including human, mouse, cat and dog [7,21]. To this date, forty-nine unique disease-causing mutations (missense mutations, deletions, nonsense mutations, splice-site mutations) in GUSB have been identified in person with MPS VII from various populations. Among these mutations, L176F is one of the most commonly reported mutations in MPSVII patients [22]. Benjamin et al. [27] first identified the L176F (Leu → Phe) of mutation in exon 3 of the beta-glucuronidase gene in the area of lysosomal targeting [23]. This high-resolution crystal structure of GUSB provided a precise mechanism for lysosomal targeting [21].

The identified variant of GUSB (NC_000007.13:g.65444706G>A) was a missense mutation in the proband. In the position 65444706 of chromosome 7, G was substituted by A, which led to change of amino acid.

In summary, mucopolysaccharidos VII as a very rare disease closely related to genetic factors. At present, foreign scholars have reported the related genes of the disease, but no further molecular genetic studies have been conducted in China. We used whole exome sequencing to identify the pathogenic genetic disease in the MPS VII patient, and rapidly identify NC_000007.13:g.65444706G>A of a point mutation in GUSB of patient. The study of the pathogenic mutations will provide theoretical basis for revealing the molecular genetic features of the disease and the prenatal diagnosis and treatment. Whole
genome sequencing is used as a supplementary method for the diagnosis of mucopolysaccharidosis VII, and at the same time it will be helpful for the targeted treatment of mucopolysaccharidosis VII.

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