

# A boy with mucopolysaccharidosis type II accompanied with a novel variation in heparan-N-sulfatase

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*To the Editor:* The mucopolysaccharidosis (MPS) disorders are a group of rare, inherited lysosomal storage disorders in which progressive cellular accumulation of glycosaminoglycans (GAGs) caused by lysosomal enzyme deficiency, leads to multi-organ dysfunction. Each kind of MPS disorder (I–IX) is caused by deficiency of a specific lysosomal enzyme and subsequent degraded GAGs fragments increase in urine, blood, and cerebral spinal fluid. MPS II, also called Hunter Syndrome (OMIM 309900), is a recessive X-linked lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase (*IDS*). The *IDS* gene is located on Xq28, contains nine exons and encodes a precursor protein of 550 amino acids.<sup>[1]</sup> More than 500 *IDS* mutations have been identified that cause MPS II in the Human Gene Mutation Database. This deficiency leads to accumulation of GAGs, including dermatan sulfate and heparan sulfate in lysosomes of the liver, spleen, connective tissue, and brain, with excretion in the urine.<sup>[2]</sup> MPS II was traditionally divided into two sub-types according to clinical severity. Individuals with the mild form may have attenuated somatic complications, short stature, survive to adulthood, and often exhibit no mental retardation. In contrast, severely affected individuals are characterized by early somatic abnormalities including progressive neurological damage, hepatosplenomegaly, progressive cardiopulmonary deterioration, skeletal deformities, and usually die of obstructive airway disease or cardiac failure before the age of 15 years.<sup>[3]</sup> Here, we describe the clinical and genetic findings of a Tibetan boy with MPS II carrying a novel variation in heparan-N-sulfatase (*SGSH*, sulfamidase). Our report also explains the impact of *IDS* mutations on enzyme activity.

The proband, a 10-year old boy, was initially identified in May 2017 in the Department of Pediatric Surgery of West China Hospital. He was the only person with the disease in

this Tibetan family and was born at home after 35 weeks of gestation with unclear birth weight and body length. He rarely cried or spoke. His short stature attracted attention at age of 3 years. In addition, he presented with unusual facial features (receding forehead, wide distance between the eyes, flat nose, full lips, and thick auricles), contractures of distal inter-phalangeal joints, claw hands [Figure 1A and 1B], short neck, abnormal gait, umbilical hernia, and hearing loss. His speech was normal but he did not like to talk. At the age of 10 years, he was severely growth retarded with a height of 113.1 cm and weight of 23.5 kg, but had a large head circumference of 55 cm. X-rays of left wrist joints showed Madelung deformity and delayed bone age [Figure 1B]. Color Doppler ultrasound of the abdomen showed no hepatosplenomegaly although abdominal distension was obvious. The boy also showed no impaired mental or psychomotor development. Neither of his parents showed any symptoms. Biochemical analysis revealed the *IDS* enzyme activity in the proband was 2.10 nmol·mg<sup>-1</sup>·4h<sup>-1</sup> (reference range >30 nmol·mg<sup>-1</sup>·4h<sup>-1</sup>). Moreover, the urinary polysaccharide toluene blue staining test of the boy was positive.

Genomic DNA from the patient was sent to KingMed Center for Clinical Laboratory, Guangzhou, China. The genes associated with MPS (I–VII) (including *IDUA*, *IDS*, *SGSH*, *NAGLU*, *HGSNAT*, *GNS*, *GALNS*, *GLB1*, *ARSB*, *GUSB*, *MAN2B1*, *MANBA*, *FUCA1*, *NAGA*, *AGA*, *GNPTAB*, *GNPTG*, *MCOLN1*, *NEU1*, *SUMF1*, *GLB1*, *GM2A*, and *HYAL1*) were screened by Sanger sequencing with Illumina ABI3500 (USA). Exon 9 of *IDS* and exon 5 of *SGSH* were validated in the proband by Sanger sequencing. The result of verification was compared with mRNA templates (*IDS*: NM\_000202.6; *SGSH*: NM\_000199.3). Two mutations were identified, including

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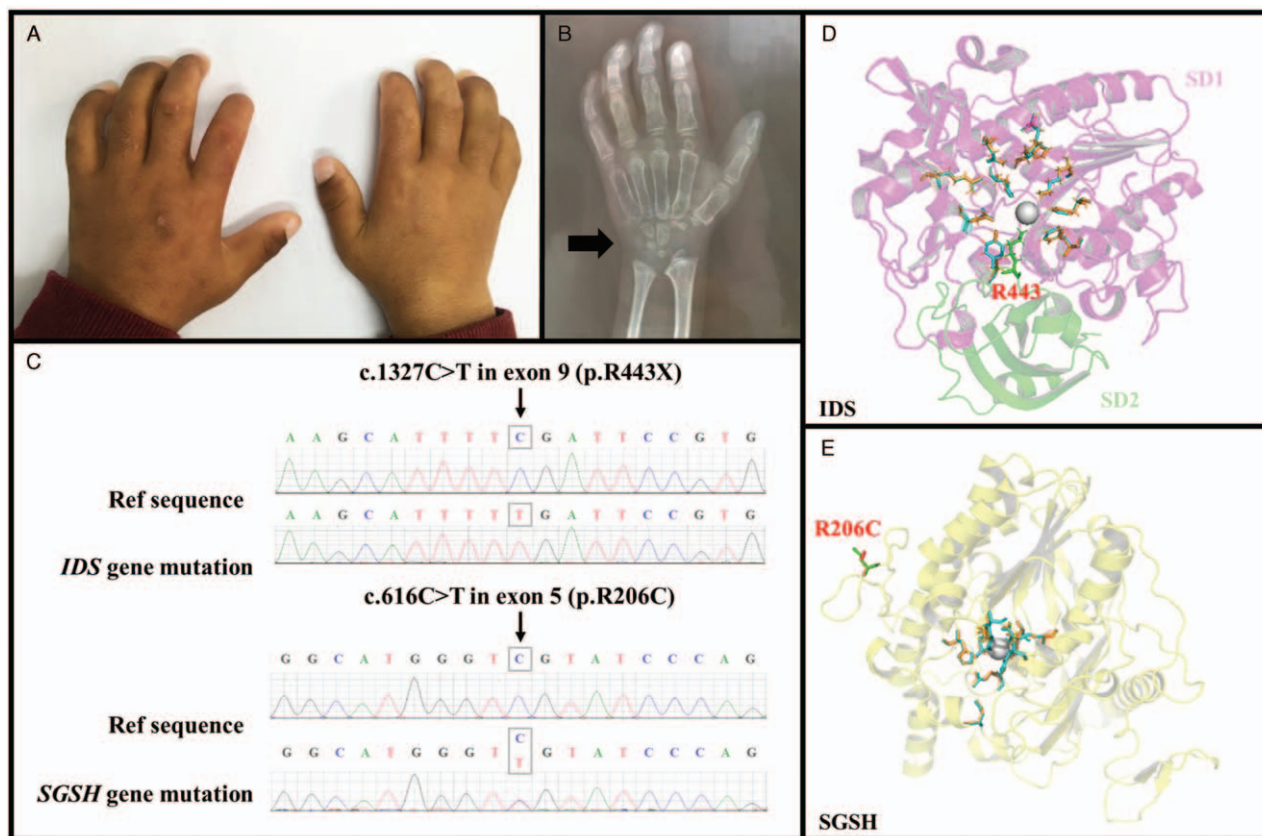
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**Figure 1:** Profile of the proband. (A) Claw hands. (B) X-ray of left hand. (C) Sequence electropherograms of *IDS* and *SGSH* mutations. (D) Comparison of the crystal structure of normal human *IDS* and the *IDS* mutation model. The crystal structure and mutation model of *IDS* are superimposed and their backbones are indicated as ribbon models. The N-terminal SD1 domain is in magenta and the C-terminal SD2 domain is represented in green. The residues involved in substrate binding are represented by cyan and orange sticks. E443X causes deletion of the SD2 domain (green) and destruction of the spatial structure of *IDS*. (E) Comparison of the crystal structure of normal human *SGSH* and the *SGSH* mutation model. R206 (verdant) is substituted by C206 (red). *IDS*: Iduronate-2-sulfatase; *SGSH*: Heparan-N-sulfatase.

one non-sense mutation c.1327C>T (p.R443X) in exon 9 of *IDS* and a novel variation c.616C>T (p.R206C) in exon 5 of *SGSH* [Figure 1C].

To explore the influence of the mutations reported in this study on protein structure and function, homology modeling of normal and mutant proteins was performed using SWISS-MODEL (Swiss Institute of Bioinformatics, Basel, Switzerland). PyMol 2.2 (DeLano Scientific LLC, San Carlos, California, USA) was used to superimpose crystal structure images (*IDS* template: 5FQL.1.A.PDB; *SGSH* template: 4MHX.1.A.PDB) and mutation models of *IDS* and *SGSH*. *IDS* crystal structure is a monomer composed of a polypeptide chain (containing residues 34–550) that forms a compact spherical  $\alpha/\beta$  sandwich fold. In general, the *IDS* backbone is divided into two sub-domains, the N-terminal SD1 (residues 34–443) forming a 42,000 heavy chain and the C-terminal SD2 (residues 455–550) corresponding to a 14,000 light chain.<sup>[4]</sup> In this patient, residues after 443 were lost, resulting in a deficient SD2 domain [Figure 1D]. Hence, enzyme activity of *IDS* was significantly affected. A second variation occurred in *SGSH*, resulting in replacement of arginine residue 206 with cysteine [Figure 1E]. However, the *SGSH* variation was heterozygous and unverified, therefore, its pathogenicity is unclear.

Developmental delay is a prominent and consistent feature of MPS II. The 10-year-old Tibetan boy in this study had significant growth retardation and his bone age was approximately 6.5 years old. The severity of the disease should primarily be determined by the type of mutation and the degree of cognitive impairment. Unfortunately, the severity of neurological symptoms in the patient had not been thoroughly assessed. We learned from the parents that the patient's academic performance is average. Indeed, patients with large deletion, rearrangement, or non-sense mutations are associated with a more severe phenotype compared with those with missense, splice-site, or insertion and insertion/deletions mutations. The recessive X-linked pathogenic variant in *IDS* reported here is a non-sense mutation c.1327C>T (p.R443X) that has been reported in Japanese, Korean, Chinese, and British patients with an attenuated type of MPS II.<sup>[5]</sup> In theory, the mutation c.1327C>T (p.R443X) results in a pre-mature stop codon and the loss of 107 amino acids from the C-terminus of *IDS*. Although the truncated protein retains the SD1 domain containing the catalytic core, it lacks a twisted four-stranded anti-parallel  $\beta$ -sheet, a short C-terminal  $\alpha$ -helix, five helical turns, and two putative N-linked glycosylation sites at codons 513 and 537.<sup>[5]</sup> The protein structure of this incomplete *IDS* is destabilized and is susceptible to proteolytic cleavage [Figure 1D].<sup>[5]</sup> Therefore, this patient

may retain a very low level of enzyme activity that causes an attenuated type of MPS II, as described in previous studies.<sup>[2,5]</sup> We identified another variation, c.616C>T (p. R206C) in *SGSH*, but its pathogenicity is unknown. MPS II is the pre-dominant form of mucopolysaccharidoses in China. The *IDS* gene is the only pathogenic gene of MPS II. Therefore, the identification of *IDS* mutations is significant and helpful for genetic counseling, pre-natal diagnosis, and treatment of the disease. In addition, this study presents features of MPS II and has explored the effect of the non-sense mutation c.1327C>T (p.R443X) on *IDS* enzyme activity.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

None

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