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SHORT COMMUNICATION

Database of the clinical phenotypes, genotypes and mutant arylsulfatase B structures in mucopolysaccharidosis type VI

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Mucopolysaccharidosis type VI (MPS VI) is a genetic disorder caused by a deficiency of arylsulfatase B (ARSB). In our previous study, we investigated the structural changes in ARSB caused by amino acid substitutions associated with MPS VI, and revealed that such structural changes in ARSB were correlated with the clinical phenotypes. To the best of our knowledge, there is no database containing the structures of mutant ARSBs. Here, we built a database of clinical phenotypes, genotypes and structures of mutant ARSBs (http://mps6-database.org). This database can be accessed via the Internet, and is user friendly being equipped with powerful computational tools. This database will be useful for a better understanding of MPS VI.
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Arylsulfatase B (ARSB, N-acetylgalactosamine-4–sulfatase, EC 3.1.6.12) catalyzes the hydrolysis of the sulfate moiety of glycosaminoglycan (GAG) dermatan sulfate.[1,2] A deficiency of ARSB, which is caused by a mutation in the *ARSB* gene located on chromosome 5 (5q13-5q14), results in the accumulation of the substrate in lysosomes of various types of tissues, leading to an autosomal recessive lysosomal storage disorder, mucopolysaccharidosis type VI (MPS VI; Maroteaux–Lamy syndrome; MIM#253200). MPS VI exhibits a broad spectrum of clinical phenotypes, from severe to attenuated forms, and patients with this disease exhibit growth retardation, a short stature, coarse faces, skeletal deformities, stiff joints, corneal clouding, respiratory difficulty, hepatosplenomegaly and cardiac abnormalities.

So far, a large number of *ARSB* gene mutations, predominantly missense ones, causing MPS VI have been identified,[1,2] and their complexity makes it difficult to understand the disease. To elucidate the mechanism underlying the disease, three-dimensional (3D) structural analysis of ARSB has been performed. For example, Garrido *et al.*[3] visualized the locations of mutations in the ARSB structure using 3D visualization software. Furthermore, our group revealed that the structural changes in ARSB caused by amino acid substitutions were correlated with the clinical phenotypes;[4] that is, a large structural change in ARSB or a structural change in the core region of ARSB tends to cause a severe form, whereas a small structural change in ARSB or a structural change on the surface of ARSB tends to cause an attenuated form. This suggests that information on structural changes in ARSB will facilitate our understanding of the disease.

In this study, we built a database of clinical phenotypes, genotypes and structures of mutant ARSBs. The information on the *ARSB* gene mutations was mainly obtained from the HGMD database (http://www.hgmd.org/),[5] and structural models of mutant ARSBs were built according to the method described previously,[4] using the crystal structure of human ARSB as a template (Protein Data Bank (PDB) code: 1FSU).[6] All researchers and clinicians can use this database (http://mps6-database.org) for free. To use all the functions of this database, JavaScript and Java Runtime Environment must be plugged in.

A total of 96 unique ARSB mutations (81 missense mutations and 15 nonsense) have been incorporated into the database so far. However, the structural data on the template ARSB from the PDB do not provide us with information about the locations of two specific missense mutations in the molecule, so mutant ARSB models for the 79 missense ones were built. To the best of our knowledge, this is the first database of the 3D structures of mutant ARSBs, and it contains: (i) comprehensive information on the gene mutations associated with MPS VI (data structure and basic statistics are presented in Supplementary data S1 and S2, respectively), (ii) tools for 3D structure visualization and (iii) tools for searching for *ARSB* gene mutations. Several tools have been installed within the database to enhance its scope. A text search tool is provided for searching selected fields of the

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MPS6 mutants list

keyword:

display items: ☑ seq ☑ str

display only missense mutation: ○ yes ◉ no

list reset

control table: redraw

id	locus	mtype	gtype	ptype	race	author	paper	note
1		missense mutation	GCG-GTG A33V			Karageorgos	(2007) Hum Mutat 28, 897	
2		missense mutation	cGAC-AAC D54N	Severe		Karageorgos	(2007) Hum Mutat 28, 897	
3		missense mutation	TGGa-TGC W57C			Karageorgos	(2007) Hum Mutat 28, 897	
4		missense mutation	cGAC-AAC D59N			Petry	(2005) J Inherit Metab Dis 28, 1027	
5		missense mutation	TCC-TTC S65F	Attenuated		Villani	(1999) Biochim Biophys Acta 1453, 185	
6		missense mutation	CTG-CAG L72Q			Isbrandt	(1996) Hum Mutat 7, 361	
7		missense mutation	CTG-CGG L72R	Severe		Petry	(2005) J Inherit Metab Dis 28, 1027	
8		missense mutation	CTG-CGG L82R			Garrido	(2007) Mol Genet Metab 92, 122	
9		missense mutation	gGAC-TAC D83Y	Attenuated		Karageorgos	(2007) Hum Mutat 28, 897	
10		missense mutation	CAGc-CAC Q88H			Petry	(2005) J Inherit Metab Dis 28, 1027	
11		**missense mutation**	**ACG-AAG T92K**			**Karageorgos**	**(2007) Hum Mutat 28, 897**	
12		missense mutation	ACG-ATG T92M			Litjens	(1996) Am J Hum Genet 58, 1127	
13		missense mutation	gCCG-TCG P93S			Petry	(2005) J Inherit Metab Dis 28, 1027	
14		missense mutation	CGG-CAG R95Q	Severe		Litjens	(1996) Am J Hum Genet 58, 1127	
15		missense mutation	AGCc-AGG S96R			Karageorgos	(2007) Hum Mutat 28, 897	

Figure 1 The page of the list of MPS VI gene mutations. The 'phenotype' is determined basically according to the original papers as described in Saito *et al.*[4]

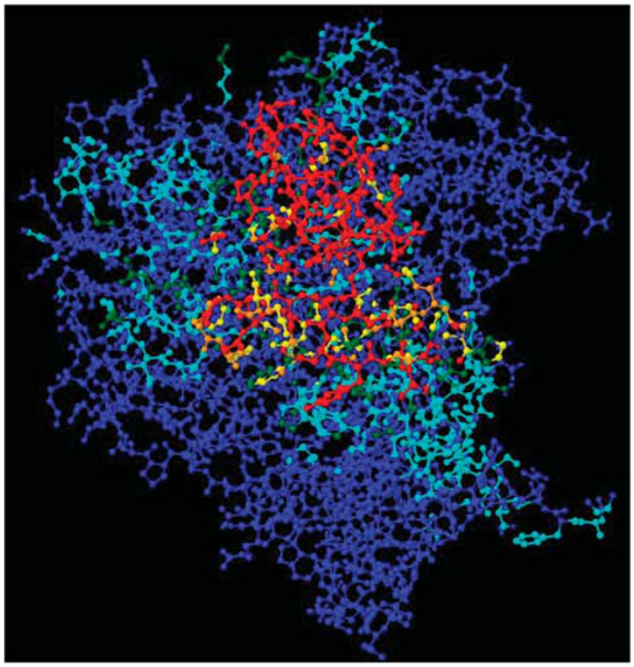

Figure 2 Color imaging of a mutant ARSB protein with a G308R amino acid substitution. Each atom of the molecule is colored according to the distance between the atom in the mutant and the corresponding atom in the wild-type structure. The colors of the atoms show the distances, as follows: blue <0.15 Å, 0.15 Å $\leqslant$ cyan <0.30 Å, 0.30 Å $\leqslant$ green <0.45 Å, 0.45 Å $\leqslant$ yellow <0.60 Å, 0.60 Å $\leqslant$ orange <0.75 Å and red $\geqslant 0.75$ Å. The colors of the atoms show the distances, as follows: blue <0.15 Å, 0.15 Å $\leqslant$ cyan <0.30 Å, 0.30 Å $\leqslant$ green <0.45 Å, 0.45 Å $\leqslant$ yellow <0.60 Å, 0.60 Å $\leqslant$ orange <0.75 Å, and red $\geqslant 0.75$ Å.

database. A control table option is incorporated for an intensive search. Using this option, users can search for MPS VI gene mutations associated with specific phenotypes. Figure 1 shows the page of the list of MPS VI gene mutations. This database also allows users to observe the 3D structures of the mutant proteins using Jmol (http://www.jmol.org), which is an open-source Java viewer for chemical structures. The database provides users with many options for visualizing the structures of mutant ARSBs. Figure 2 presents a page concerning the mutant ARSB structure with a G308R amino acid substitution, as an example.

In conclusion, we built a database for MPS VI. This database will help users to understand MPS VI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Journal of Human Genetics website (http://www.nature.com/jhg)