

## SHORT COMMUNICATION

# Fabry-database.org: database of the clinical phenotypes, genotypes and mutant $\alpha$ -galactosidase A structures in Fabry disease

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Fabry disease is a genetic disorder caused by a deficiency of  $\alpha$ -galactosidase A (GLA). In our previous studies, we structurally investigated Fabry disease using a structural analysis system, and revealed that structural changes in GLA are very important for understanding the molecular basis of this disease. To the best of our knowledge, there is no database including the structures of mutant GLAs. Herein, we constructed a database of clinical phenotypes, genotypes and structures of mutant GLAs. This database can be accessed as 'fabry-database.org', and is user friendly, being equipped with powerful computational tools. This database will help researchers and clinicians who study Fabry disease.

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Fabry disease (MIM 3010500) is an X-linked genetic disease resulting from a deficiency of  $\alpha$ -galactosidase A (GLA, EC 3.2.1.22), and exhibits a wide clinical spectrum, from the early-onset severe 'classic' form to the late-onset mild 'variant' one.<sup>1</sup> Recently, the results of newborn screening revealed that the incidence of Fabry disease is unexpectedly high,<sup>2–4</sup> and that the genotypes of patients with this disease are quite heterogeneous.<sup>5</sup>

Previously, we constructed structural models of mutant GLAs resulting from 161 Fabry missense mutations, and examined the correlation between structural changes in GLA and the clinical and biochemical phenotypes of Fabry disease.<sup>6</sup> Recently, we conducted further structural investigation on Fabry disease using a structural analysis system and revealed that structural changes in GLA are very important for understanding the molecular basis of this disease.<sup>5</sup>

To the best of our knowledge, there is no database including the structures of mutant GLAs. In order to help researchers and clinicians who study Fabry disease, we built a database of clinical phenotypes, genotypes and structures of mutant GLAs. This database can be accessed as 'fabry-database.org', and is user-friendly, being equipped with powerful computational tools like Jmol, which is an open-source Java viewer for chemical structures in 3D (<http://www.jmol.org>). The web interface and applications are shown in Supplementary Information S1.

Fabry-database.org contains (i) comprehensive information on GLA mutations, (ii) tools for three-dimensional structure visualization and (iii) tools to search for GLA mutations. A total of 504 unique GLA mutations have been incorporated into the database so far. The

GLA mutation statistics and the data structure of fabry-database.org are shown in Table 1 and Supplementary Information S2, respectively.

Several tools have been equipped within the database to enhance its scope. The following are the main web tools integrated into fabry-database.org (Figure 1). A text search tool is provided for searching selected fields of the database. A control table option is incorporated for an intensive search. Using this option, users can search for Fabry mutations that are connected with specific phenotypes. Fabry-database.org allows users to display the three-dimensional structures of molecules using Jmol. Users are provided with many options for visualizing the structures of mutant GLAs. Figure 2 represents the pages concerning the structure of a mutant GLA with the T100R amino-acid substitution, as an example. As a structural change in GLA

**Table 1** Gene mutations causing Fabry disease

Mutation type	Number of entries
Missense mutation	289
Deletion	91
Nonsense mutation	55
Insertion	28
Aberrant splicing	26
Others	15
Total	504

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Fabry mutants list

keyword:

display items:  seq  str

display only missense mutation:  yes  no

control table:

id	locus	mutype	gtype	gprype	race	author	paper	note
1	5'>	deletion	Del 4.6kb (5'-Int 2)	classic		Okumiyama T	J Clin Invest 1969, 83: 1390-9	
2	5'>	others	G->A (#39)			Fitzmaurice TF	J Inher Metab Dis 1997, 20: 643-57	
3	Exon 1	others	G->A (#30)			Davies JP	J Med Genet 1993, 30: 658-63	(G->A at-30)
4	Exon 1	others	G->A (#12)			Davies JP	J Med Genet 1993, 30: 658-63	(G->A at-12)
5	Exon 1	others	C->T (#10)			Davies JP	J Med Genet 1993, 30: 658-63	(1170C->T)
6	Exon 1	others	C->T (#10) + Del3b (#1072-1074)	classic	Japanese	Takata T	Brain Dev Jpn 1997, 19: 111-6	
7	Exon 1	deletion	Del 1b (#9) + Del 1b (#9)			Altarescu GM	Clin Genet 2001, 60: 46-51	(1bp del 9; (#9))
8	Exon 1	missense mutation	MLT	classic		Eng CM	Mol Med 1997, 3: 174-82	
9	Exon 1	missense mutation	MLI	classic		Blanch LC	Hum Mutat 1996, 8: 38-43	
10	Exon 1	missense mutation	MLR	classic		Shabbeer J	Mol Genet Metab 2002, 76: 23-30	
11	Exon 1	deletion	Del 1b (#6)			Altarescu GM	Clin Genet 2001, 60: 46-51	(1bp del 6)
12	Exon 1	deletion	Del 1b (#9)			Altarescu GM	Clin Genet 2001, 60: 46-51	(1bp del 9)
13	Exon 1	nonsense mutation	P6X			Altarescu GM	Clin Genet 2001, 60: 46-51	
14	Exon 1	deletion	Del 1b (#18)	classic		Shabbeer J	Hum Mutat 2005, 25: 299-305	(c18delA)
15	Exon 1	deletion	Del 26b (#21-46)			Altarescu GM	Clin Genet 2001, 60: 46-51	(1bp del 21)
16	Exon 1	deletion	Del 1b (#26)	classic	English	Eng CM	Hum Mol Genet 1994, 3: 1795-9	(25del1)
17	Exon 1	deletion	Del 1b (#29)		Brazilian	Ashton-Prolla P	Am J Med Genet 1999, 11: 420-4	(30delG)
18	Exon 1	deletion	Del 24b (#34-57)	hetero		Whybra C	J Inher Metab Dis 2002, 24: 715-24	(34del24)
19	Exon 1	deletion	Del 13b (#35-47)	classic		Topaloglu AK	Mol Med 1999, 5: 806-811	(35del3)
20	Exon 1	missense mutation	L14P	classic	Chinese	Tse KC	Nephrol Dia Transplant 2003, 18: 182-6	

Figure 1 List of Fabry mutations. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

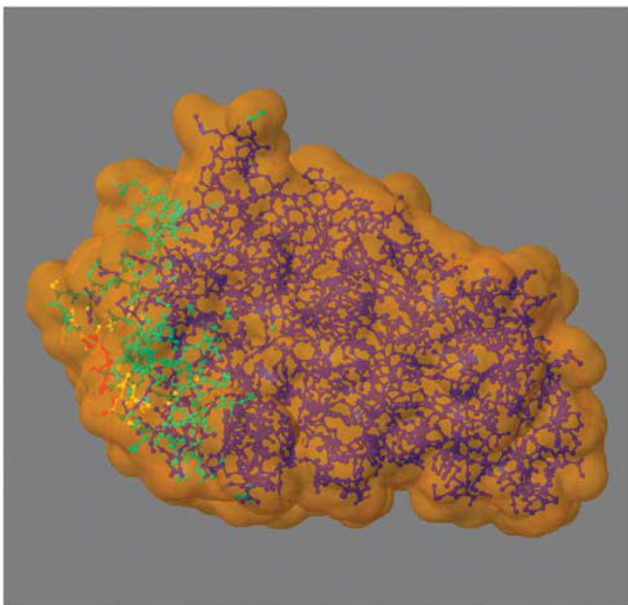


Figure 2 Structure: color imaging of the T100R mutation by means of the solvent-accessible surface area.

should be related to genotype expression and the outcome of Fabry disease,<sup>5,6</sup> this database will help researchers and clinicians.

The major limitation for expanding this database is that the information on Fabry mutations is too scattered. A lot of literature

search is required to further expand it. In the near future, we are hopeful of expanding the database quantitatively to cover all possible amino-acid mutations. This database will be updated manually as soon as enough data become available.

In conclusion, we constructed fabry-database.org, which is available at <http://www.fabry-database.org>. To access fabry-database.org, the World Wide Web access is a prerequisite. For using all the features of fabry-database.org optimally, plugging in the JavaScript and Java Runtime Environment must be enabled.

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- Desnick, R. J., Ioannou, Y. A. & Eng, C. M. Alpha-galactosidase A deficiency: Fabry disease, in *The Metabolic and Molecular Bases of Inherited Disease* 8th edn (eds Scriver, C.R., Beaudet, A.L., Sly, W.S. & Valle, D.) 3733–3774 (McGraw-Hill, New York, NY, 2001).
- Spada, M., Pagliardini, S., Yasuda, M., Tukul, T., Thiagarajan, G., Sakuraba, H. *et al*. High incidence of later-onset Fabry disease revealed by newborn screening. *Am. J. Hum. Genet.* **79**, 31–40 (2006).
- Hwu, W. L., Chien, Y. H., Lee, N. C., Chiang, S. C., Dobrovolsky, R., Huang, A. C. *et al*. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). *Hum. Mutat.* **30**, 1397–1405 (2009).
- Lee, B. H., Heo, S. H., Kim, G.-W., Park, J.-Y., Kim, W.-S., Kang, D H *et al*. Mutations of the *GLA* gene in Korean patients with Fabry disease and frequency of the E66Q allele as a functional variant in Korean newborns. *J. Hum. Genet.* **55**, 512–517 (2010).
- Sugawara, K., Ohno, K., Saito, S. & Sakuraba, H. Structural characterization of mutant alpha-galactosidases causing Fabry disease. *J. Hum. Genet.* **53**, 812–824 (2008).
- Matsuzawa, F., Aikawa, S., Doi, H., Okumiyama, T. & Sakuraba, H. Fabry disease: correlation between structural changes in alpha-galactosidase, and clinical and biochemical phenotypes. *Hum. Genet.* **117**, 317–328 (2005).

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