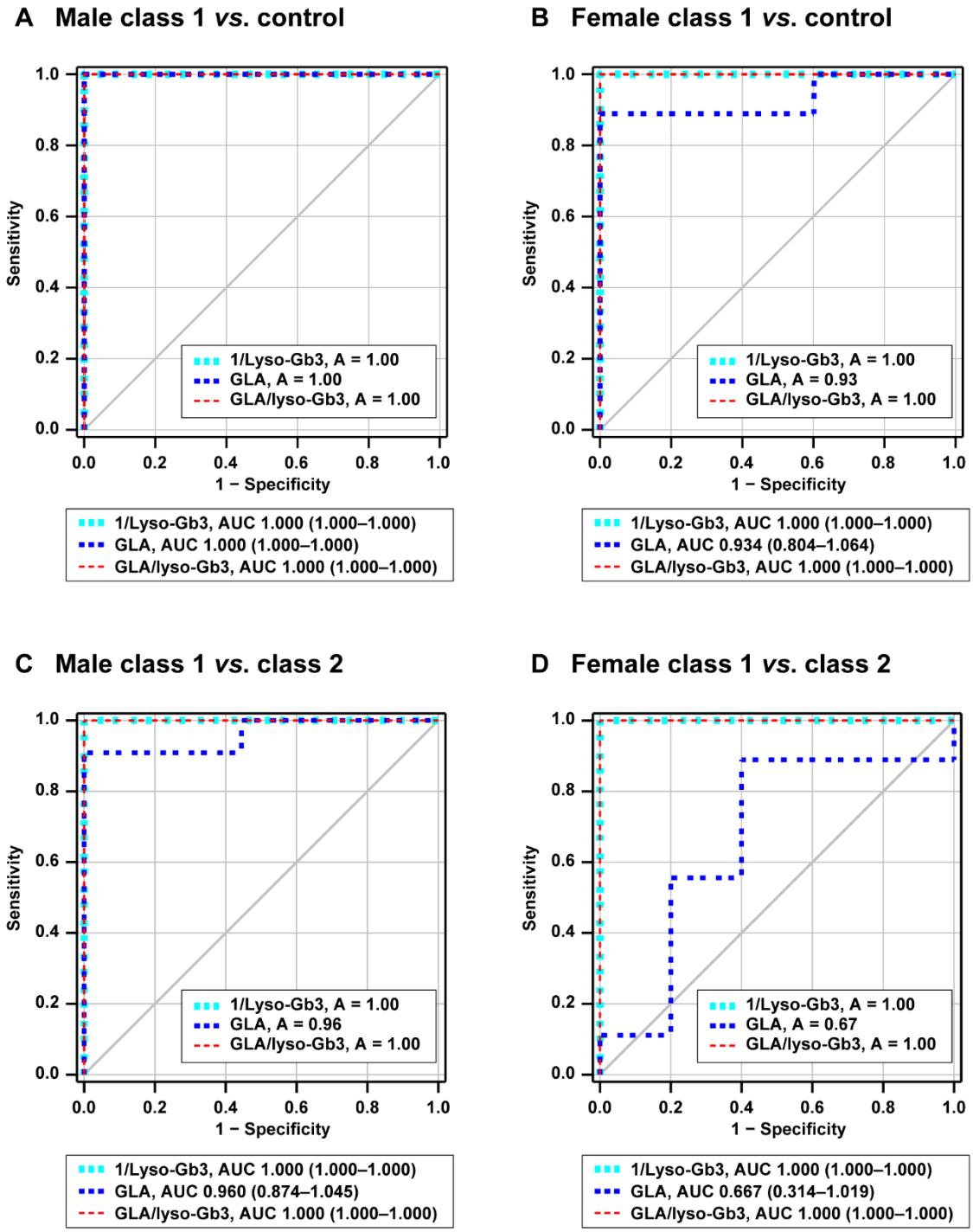
Plasma Globotriaosylsphingosine and α-Galactosidase A Activity as a Combined Screening Biomarker for Fabry Disease in a Large Japanese Cohort

1. SUPPLEMENTARY FIGURE



Supplementary Figure S1. Comparison of receiver operating characteristic (ROC) curves for plasma 1/lyso-Gb3 levels, GLA activity, and GLA/lyso-Gb3 ratio for male and female patients enrolled from 2014 to 2016. When plasma lyso-Gb3 values were less than the detection limit of the assay (0.01 nmol/h/mL), a value of 0 ng/mL was used to represent the lyso-Gb3 levels in the statistical analysis. (**A**)

Discrimination between male patients with a class 1 variant (n = 11) and controls (n = 3243). Because 156 of the 3399 control males had a lyso-Gb3 level of 0 (see Figure 4A), these patients were excluded from the analysis. (**B**) Discrimination between female patients with a class 1 variant (n = 9) and controls (n = 2089). Because 123 of the 2212 control males had a lyso-Gb3 level of 0 (see Figure 4C), these patients were excluded from the analysis. (**C**) Discrimination between male patients with class 1 (n = 11) and class 2 (n = 9) variants. Because 1 of the 10 class 2 males had a lyso-Gb3 level of 0 (see Figure 4A), this patient was excluded from the analysis. (**D**) Discrimination between female patients with class 1 (n = 9) and class 2 (n = 5) variants.

2. SUPPLEMENTARY TABLE

Supplementary Table S1. *GLA* variants identified by screening for Fabry disease in young patients with cerebrovascular diseases.

References (year of publication)	Participants (*n*) Males	Females	Total	Fabry disease diagnosis (*n*)	*GLA* variants	Class 1 variants (*n*)
Rolfs *et al*. (2005)[S1]	432	289	721	28	Not reported	0
Brouns *et al*. (2007)[S2]	64	39	103	0	None	0
Wozniak *et al*. (2010)[S3]	558	0	558	1	p.Ala143Thr (FD-causing)[1]	0
				0	p.Asp313Tyr (polymorphism)[1]	0
Baptista *et al*. (2010)[S4]	300	193	493	2	c.–44C>T	0
				6	p.Arg118Cys	0
				6	p.Asp313Tyr	0
Brouns *et al*. (2010)[S5]	–	–	842	1	p.Ser126Gly[1]	0
				2	p.Ala143Thr[1]	0
				3	p.Asp313Tyr[1]	0
Sarikaya *et al*. (2012)[S6]	102	48	150	0	None	0
Marquardt *et al*. (2012)[S7]	85	69	154	0	None[2]	0
Rolfs *et al*. (2013)[S8]			5023	27[3]		0
					p.Asp83Asn[1]	
					p.Ser102Leu[1]	
					p.Arg118Cys[1]	
					p.Ser126Gly[1]	

					p.Ala143Thr[1] p.Val316Ile[1] p.Leu415Phe[1] p.Glu418Gly[1]	
Dubuc *et al*. (2013)[S9]	55	45	100	1	c.–10C>T, c.370–81_370–77delCAGCC, c.640–16A>G, c.1000–22C>T	0
Fancellu *et al*. (2015)[S10]	–	–	148	1	p.Arg227Gln[1,4]	1
				1	p.Asp313Tyr[1]	0
Lanthier *et al*. (2017)[S11]	218	179	397	1	p.Arg118Cys	0
				0	p.Asp313Tyr (neutral)	0
				0	c.–10C>T, c.370–81_370–77delCAGCC, c.640–16A>G, c.1000–22C>T (neutral)	0
				0	c.1000–22C>T, c.1290+43A>G (neutral)	0
Kinoshita *et al*. (2018)[S12]	394	120	516	0	p.Glu66Gln (non-pathogenic)[1]	0
Maruyama *et al*. (2019)[S13]	281	220	501[5]	0	None	0

The methods of *GLA* analyses:

[1] Only the protein variants were described with no description of the method of gene analysis; therefore, the DNA variants were not classified based on the Human Genome Variation Society recommendations.

[2] Five patients who had the *GLA* variant p.Asp313Tyr were excluded because they were over 60 years old.

[3] The number of each *GLA* variant was not described.

[4] The male proband with classic Fabry disease (p.Arg227Gln) exhibited acroparesthesia, multiple white matter lesions, and severe cardiac and renal involvement.

[5] Patients with cerebrovascular disease referred from neurology.

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4. SUPPLEMENTARY ACKNOWLEDGMENTS

The following physicians and centers participated in this study: Kazuhiro Aoki, Department of Cardiology, National Tokyo Hospital; Kenju Aoki, Neurological Center Agano Hospital; Nami Araya, Department of Pediatrics, Iwate Medical University; Tomoki Asai, Dialysis Center, Sagami Junkanki Clinic; Mio Ebato, Division of Cardiology, Showa University Fujigaoka Hospital; Kaoru Endo, Division of Neurology, Sendai City Hospital; Akihiro Fujii, Department of Neurology, Saiseikai Shiga Hospital; Makoto Furugen, Miyazaki Medical Association Hospital Cardiovascular Center; Nobuyuki Furuta, Division of Clinical Laboratory, Gifu University Hospital; Shoji Haruta, Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center; Tsuguhisa Hatano, Hatano Clinic, and Department of Cardiology Tokyo Medical University; Kyoko Hazama, Department of Neurology, Gunma Children's Medical Center; Shuma Hirashio, Department of Nephrology, Hiroshima University Hospital; Yukio Hiroi, Department of Cardiology, National Center for Global Health and Medicine; Manabu Hishida, Department of Nephrology, Nagoya University Hospital; Taro Horino, Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University; Moritake Iguchi, Department of Cardiology, National Hospital Organization Kyoto Medical Center; Takeshi Inoue, Department of Pediatrics, Dokkyo Medical University Saitama Medical Center; Ayano Inui, Department of Pediatric Hepatology and Gastroenterology, Saiseikai Yokohamashi Tobu Hospital; Koji Ishiguro, Department of Neurology, Moteki Neurosurgery; Tetsuya Ito, Department of Pediatrics, Fujita Health University School of Medicine; Manabu Iwata, Hirosaki Stroke and Rehabilitation Center; Misako Kaido, Department of Neurology, Sakai City Medical Center; Kenji Kamiyama, Department of Neurosurgery, Nakamura Memorial Hospital; Bunta Kato, Department of Neurology, St. Marianna University School of Medicine, Yokohama City Seibu Hospital; Sanami Kawada, Department of Neurological Surgery, Okayama Kyokuto Hospital; Yuriko Kikkawa, Department of Neurology, Japanese Red Cross Society Narita Hospital; Masahiro Kikuchi, Department of Pediatrics, Hitachi General Hospital; Yukihiro Kimura, Division of Nephrology, Department of Internal Medicine, Gifu Municipal Hospital; Junya Kobayashi, Department of Vascular Neurology, National Hospital Organization Osaka Minami Medical Center; Yuji Koide, Department of Cardiovascular Medicine, Nagasaki University Hospital; Tomoyuki Kono, Department of Neurology, Kobe City Medical Center General Hospital; Toru Kubo, Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University; Akiko Kumagai, Department of Internal Medicine, Division of Cardiology, Iwate Medical University; Yasuhiro Kumai, Department of Cerebrovascular Disease

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